The New England
Journal of Medicine

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Volume 232 MARCH 22, 1945 Number 12

THE TREATMENT OF URETERS INJURED DURING GYNECOLOGIC OPERATIONS

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ACCIDENTAL injury of a ureter is the most frequent serious complication of gynecologic pelvic operations. This fact was brought to our attention by the occurrence of 7 ureteral injuries in 590 total hysterectomies and 1 ureteral injury in 170 supravaginal hysterectomies done during a five-year period at the Massachusetts General Hospital. These 8 cases will serve to illustrate the type of injuries that occur and the surgical principles and procedures to be followed in repairing them.

PRINCIPLES OF TREATMENT

Although each patient must be treated according to the circumstances of the case, there are certain important principles that should be observed when dealing with the problem of the damaged ureter. First, the immediate recognition of the injury is of the utmost importance. This is especially true since proper treatment at the time of operation may result in a successful anastomosis, with hospitalization no longer than that required for the routine uncomplicated procedure. In the 8 cases reviewed herein, injury was noted at time of operation in 4. Three of these patients did well; the fourth developed a urinary fistula and a pelvic abscess and later came to nephrectomy. Secondly, every effort should be made to preserve the kidney function on the side of the injured ureter until the function of the other side can be determined. Palpation is not an adequate means of determining renal function, and the sacrifice of a kidney by ligation or nephrectomy without knowledge of the status of the remaining kidney is unwise. Preservation of the kidney may be accomplished by nephrostomy, skin ureterostomy or transplantation of the ureter into the bowel or bladder. The technic of such transplantation will be discussed later. The third important principle is that all ureteral anastomosis should be done over an indwelling nylon or rubber ureteral catheter. The catheter serves as a splint during the healing of the ureter and also acts to decompress the kidney pelvis, preventing distention at the site of the anastomosis. The indwelling catheter has proved itself to be the most vital single factor in successful anastomosis. It should remain in place for seven or eight days after operation.

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TREATMENT AT TIME OF INJURY

The Incised or Ligated Ureter

Following the principle of repair at the time of the operation, an end-to-end anastomosis is indicated. The injured portion of the ureter is excised, and the two ends of the ureter are freed to provide adequate material, both proximally and distally, with which to work. A nylon ureteral catheter is introduced up to the kidney pelvis and the distal end is placed in the bladder. The catheter should be partially drawn out during cystoscopy at the end of the operation and attached to the thigh. The two ends of the cut ureter are approximated by suturing them around the catheter by the use of mattress sutures of fine silk, cotton or catgut. The area of the anastomosis is drained retroperitoneally through a stab wound in the flank by means of an empty Miller wick.

Bump and Crowe[1] in 1929 reported on their experience with end-to-end ureteral anastomoses in dogs. They anastomosed over one catheter and decompressed the proximal ureter with another brought out through a stab wound in the flank. Without the catheters their anastomoses resulted in fistulas and hydronephrosis. Curtis[2] in 1929 reported a case with successful anastomosis by this method. Dr. Fletcher H. Colby, in a personal communication, has advised a proximal decompression of the ureter with a small rubber catheter, omitting the inlying ureteral catheter. Proximal decompression has not been used in our cases.

Three of the 8 cases illustrate the treatment of the incised or ligated ureter. These are reported below.

CASE 1. G. P., a 47-year-old quartipara, had a fibroid uterus that had grown two thirds of the way to the umbilicus. At operation hemorrhage occurred from varices in the left broad ligament, and the ureter was clamped and cut 12 cm.

from the bladder. Both ends of the ureter were freed and anastomosed end to end over a ureteral catheter. Five mattress sutures of silk were used. The area of the anastomosis was drained through a stab wound in the flank. The catheter came out on the 4th day, and urine drained from the flank wound for 6 days. A slight hydronephrosis was demonstrated by intravenous pyelogram but later disappeared. An intravenous pyelogram 1 year later was normal.

CASE 2. E. D., a 47-year-old primipara, had endometriosis involving the ovaries and the posterior cul-de-sac. The left ureter was injured as the uterine vessels were being tied during the course of a total hysterectomy and bilateral salpingo-oophorectomy. A sleeve type of anastomosis was done over an inlying catheter, the distal end being placed inside the proximal end and secured by arterial silk. The area was drained by an empty Miller wick through a stab wound in the flank. The catheter came out on the 4th day, resulting in a ureterovaginal fistula, which healed in 17 days. At that time a marked hydronephrosis was demonstrated by intravenous pyelogram, but within 6 weeks an intravenous pyelogram was normal.

CASE 3. E. D., a 41-year-old, unmarried woman, had a fibroid tumor the size of a 7-month pregnancy. During the hysterectomy the left ureter was ligated when the uterosacral ligaments were clamped and cut. The damaged ureter was freed, and the ligature removed. After the uterus had been removed a sleeve type of anastomosis was done, the distal end of the ureter being placed inside the proximal end and held in place with three No. 00 chromic-catgut stitches. A cuff of peritoneum was sutured around the site of the anastomosis. The area was drained retroperitoneally, the wick being brought out through the left flank. A ureteral catheter was not used. Urine drained copiously from the stab wound for 2 weeks. During the 3rd week after operation a large abscess, accompanied by pyelonephritis with chills and fever, developed in the left lower quadrant of the abdomen. Re-exploration 7 weeks later demonstrated that the upper end of the left ureter ended in the abscess cavity; the distal section was not identified. A left nephrectomy was performed, recovery from which was uneventful.

Comment. This case, the only one of the 3 reported that was done without a ureteral catheter, demonstrates the dangers and difficulties encountered when a ureteral catheter is not used.

The Resected Ureter

Repair of the resected ureter is a problem. End-to-end anastomosis is usually impossible, so that one of the following methods must be used: ureterovesical transplant, ureterosigmoidal anastomosis, skin ureterostomy or ligation of the distal and proximal ends of the ureter. Nephrectomy must occasionally be resorted to.

Ureterovesical transplant. Ureterovesical transplant is the most satisfactory procedure. The cut end of the ureter is freed, the bladder is mobilized, and the free end is measured against the site of implantation to make certain that suturing is possible without tension on the ureter. To avoid strain resulting from bladder distention, a site as low as possible on the bladder should be chosen. An incision through the detrusor muscle and mucosa is made, and the ureter, which has been split for suturing, is brought through it into the bladder. The two flaps are then sutured to the bladder mucosa and the bladder muscle is closed about the ureter, one of the stitches catching the adventitia to help hold it in place. The bladder wall is then drawn about the ureter in such a way as to afford an oblique entrance into the bladder. The operative site is drained with a Penrose drain. Bladder distention is avoided by using a suprapubic drain or an indwelling urethral catheter for as long as ten days following operation. This is a safe procedure if the ureter will reach the bladder without tension.

Ureterosigmoidal anastomosis. If the resection of the ureter has been high, ureterosigmoidal anastomosis may be indicated. This method of preserving kidney function is a difficult technical procedure and is frequently complicated by sepsis. It should not be attempted by the inexperienced surgeon, since skin ureterostomy is safer.

The technic of ureterosigmoidal anastomosis was standardized by Coffey[3] in 1928. There are many modifications of his method, but his principle of a valvelike action on the ureteral wall as it passes tangentially through the bowel wall is the important technical feature of the operation. The ureter is exposed and the sigmoid is brought over to it, the site of implantation being as low in the bowel as possible without tension. An incision 4 cm. long is made through the serosa of the bowel and through the muscularis to the submucosa, the latter being stripped from the muscularis over a small area so that the ureter will have a place to lie. The segment of bowel is clamped above and below with rubber-covered clamps. A tiny incision is made in the mucosa with a cautery at the lower end of the prepared area. A stitch is attached to the free end of the ureter, and the needle is passed through the mucosal incision along a grooved director. The needle and stitch are brought out through the bowel wall, and by traction the ureter is pulled within the sigmoid. The ureter is held by placing a stitch through the peritoneum and muscularis, which catches a small bit of ureteral wall. The muscularis and peritoneum are closed with interrupted catgut.

Skin ureterostomy. A simple procedure to preserve kidney function, and one that adds little to the operation, is skin ureterostomy. The sectioned ureter is freed above the injury. Care is taken to preserve the loose areola tissue around the ureter so as to maintain its blood supply. The lateral peritoneum is dissected free, and the ureter is brought out through a stab wound on the anterior abdominal wall at the level of and medial to the anterior superior spine. The ureter is not stitched to the peritoneum or fascia but is fastened to the skin.

Ligation of ureter. A fourth possibility in the care of resected ureter is ligation. If previous urologic studies have shown good function of both kidneys without infection, ligation is probably the quickest and easiest procedure, although the chance must be taken that aseptic necrosis will follow ligation. Barney[4] in 1912 demonstrated experimentally that not all ligated ureters result in an aseptic necrosis. Hepler[5] in 1940 found that 3 per cent of patients so treated died, 24 per cent developed urinary fistulas, and 15 per cent ultimately had to have nephrectomy. Peacock[6] in 1941 reported a series of 8 patients so

treated, 2 of whom died as a result of fistula and sepsis. He advocates immediate nephrectomy, which may be safer than ligation.

The present series includes the following example of successful ligation.

CASE 4. M. M., a 50-year-old bipara, was admitted because of an abdominal mass extending halfway to the umbilicus. At operation a large fibroid was found, with the left tube and ovary thinned out over the body of the tumor. The left ureter was in the posterior sheath of the broad ligament, and a large section was inadvertently excised. Both ends of the excised ureter were ligated and the total hysterectomy was completed. After operation the temperature rose daily to 101°F. but subsided on the 8th day. The urinary output was good. The nonprotein nitrogen rose to 44 mg. per 100 cc., but fell to 20 mg. on the 14th day. The patient was discharged on the 15th postoperative day and was well at follow-up 1 year later.

TREATMENT AFTER OPERATION

Recognition of ureteral injury after operation is a surgical as well as a urologic problem. The methods of meeting this complication should be known to both the surgeon and the gynecologist.

Bilateral ligation may be diagnosed by anuria and a rising nonprotein nitrogen. Cystoscopy demonstrates the blocked ureters. For this reason, the urinary output of gynecologic patients should be carefully followed. Prompt relief of bilateral ureteral obstruction is necessary, and nephrostomy is the quickest and safest procedure. This drains the blocked kidneys and tides the patient over her acute difficulty. She can then be observed to see whether the catgut ties are dissolving, thus relieving the ureteral obstructions. Subsequent therapy depends on circumstances. Deligation may be attempted, but the operative mortality is high, and the risk of subjecting the patient to immediate postoperative re-exploration is unwarranted.

Injury to one ureter by ligature, unrecognized at the time of operation, is usually revealed by the development of a ureterovaginal fistula.

These fistulas ordinarily appear ten days to three weeks after operation. Some of them close spontaneously, and such an event should be awaited; failing this, treatment must be considered. Subsidence of local inflammatory processes around the site of the fistula is necessary, since an attempt to close it before resolution will be futile. In elderly women with a ureterovaginal fistula together with sepsis, nephrectomy, although sacrificing the kidney, is both quick and safe. The following case in this series was so treated successfully.

CASE 5. C. G., a 63-year-old unmarried woman, developed a ureterovaginal fistula following hysterectomy for endometrial cancer. During operation it was necessary to stop bleeding from the left corner of the vagina by a figure-of-eight stitch. The fistula, which was first noticed on the 8th postoperative day, failed to close of its own accord. Considering the patient's age, her disease and the fact that the other kidney functioned well, a nephrectomy was done. The convalescence was satisfactory, and the patient has remained well for the 2 years during which she had been followed by the Tumor Clinic.

Another reason for nephrectomy for ureterovaginal fistula was found in Case 3, discussed above. This patient's left ureter was anastomosed end to end — unsuccessfully. There was profuse drainage of urine through the stab wound and some vaginal drainage. A pelvic abscess formed and was drained through the stab wound. Seven weeks after operation the patient was still seriously ill. There was a marked hydronephrosis as demonstrated by intravenous pyelogram, and the temperature reached 104°F. daily. Re-exploration demonstrated that the left ureter ended in the abscess cavity; the distal end was not identified. A nephrectomy was done and the pelvic sepsis subsided. Recovery was rapid and uneventful, and the patient was free of symptoms at the end of three months.

Some ureterovaginal fistulas develop late and are accompanied by relatively little sepsis. In this event, exploration of the site of the ureteral injury is indicated, and ureterovesical transplantation is usually possible. This alternative is preferable to nephrectomy. Two cases, described below, were successfully treated in this manner.

CASE 6. M. G., a 35-year-old nulliparous woman, had severe vaginal bleeding of 6 weeks' duration and an enlarged uterus. A total hysterectomy was done, and on the 15th postoperative day a fistula was noted and cystoscopy demonstrated a blocked ureter on the right side. One month later, exploration showed the right ureter to be involved in scar about 5 cm. from the bladder. A ureterovesical transplant was done and the bladder was drained suprapubically. After operation an intravenous pyelogram demonstrated a slight hydronephrosis on the right; this subsequently subsided, and the patient was well 4 years after operation.

CASE 7. A. H., a 49-year-old nulliparous woman had had a supravaginal hysterectomy for the removal of a large fibroid in the right broad ligament. The operation was accomplished with some difficulty. A right ureterovaginal fistula developed on the 20th postoperative day, the block being 4 cm. from the ureteral orifice. Two months later, a ureterocystostomy was done, the dilated right ureter being implanted without undue tension. The convalescence was uneventful, and an intravenous pyelogram 4 months later showed good kidney function. Two years later the patient was still well.

If the site of the ureterovaginal fistula is high and at exploration the cut end of the ureter will not reach the bladder, ureterointestinal anastomosis should be considered. In cases in which the ureter is dilated and pyelonephritis is present, nephrectomy is a safer operation than ureterointestinal anastomosis, the latter being contraindicated in the presence of pyelonephritis.

There is still another type of injury not recognized at operation that should be mentioned, namely, the ligated ureter that does not cause a fistula. How many such cases there are is unknown. Newell[7] in 1939 reported 15 cases of ureteral injury; 6 of these patients had unilateral ligations that were unsuspected until discovery at autopsy.

All patients who have a difficult time after operation should be watched for ureteral difficulties. Severe costovertebral pain may be caused by a

blocked ureter, and an intravenous pyelogram should be done in this event to prove or disprove the diagnosis. The following case is illustrative.

CASE 8. M. L., a 49-year-old nulliparous woman, had a total hysterectomy for fibroids. A daily temperature of 102°F. was attributed to a draining ear until she complained of costovertebral angle tenderness. An intravenous pyelogram demonstrated that the left ureter was blocked 5 cm. from the bladder. The patient's condition improved until the 20th postoperative day, when she lapsed into a coma and died. Autopsy showed that the left ureter was tied off by a catgut ligature; that was also a massive cerebral hemorrhage.

SUMMARY AND CONCLUSIONS

Eight cases of ureteral injury among 760 hysterectomies performed at the Massachusetts General Hospital are discussed.

The following conclusions are drawn: immediate recognition of the injury is essential; kidney function should be preserved whenever possible; all ureteral anastomoses should be done end to end over a ureteral catheter; bilateral ligation is best treated by bilateral nephrostomies; and ureterovaginal fistulas that do not close spontaneously should be repaired either by ureteral transplant to the bladder or bowel or by nephrectomy.

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THE TIME FACTOR IN THE DEVELOPMENT OF COMPLICATIONS OF GALLSTONES*

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IF GALLSTONES remain in the gall bladder, according to Cheever,[1] "sooner or later, if their host lives long enough, they will cause damage of a serious nature." With this statement there can be only general accord, but the phrase "sooner or later" is vague. The following statistical study was undertaken with the hope of establishing a more definite time relation between the original disease and the sequelae.

It is generally acknowledged that gallstones may exist for many years without giving rise to symptoms,[2] but once they have been demonstrated, one is obliged to assume that eventually such sequelae as acute cholecystitis, acute pancreatitis, common-duct stones and carcinoma of the gall bladder may develop. Acute cholecystitis and acute pancreatitis may occur when no stones are to be found in the gall bladder; stones may even occur in the common duct with no calculi present in the gall bladder. The complications and sequelae of cholelithiasis, however, cannot be anticipated if the existence of stones in the gall bladder has not been established. Accordingly, the time factor for the development of biliary complications must resolve itself into the time lapse between the onset of primary symptoms or demonstration of stones and the clinical onset of these complications.

A better understanding of this time factor would be of great assistance in treating today's civilians. Gallstones, which are estimated to effect approximately one third of the adult population,[3,4] occur most frequently in persons over forty years old, and these are the people so essential on the home front. The older the age group, the higher is the incidence of gallstones. Lee has stated[5]: "Gallstones . . . increase in frequency with advancing birthdays, and it is likely that if people lived to be one hundred and twenty they all would have gallstones. Certainly, autopsies performed on people of eighty or over show almost uniformly the presence of gallstones." Moreover, as I[6] pointed out in a previous paper, operation for gallstones may have to be deferred during the war because of the shortage of nursing and professional services, hospital accommodations and domestic help to care for children, as well as the desire of workers to remain constantly on their jobs.

A study has therefore been made of 260 private records of operation for gallstones. The average

*Presented at the Section of Surgery, American Medical Association, June 15, 1944

duration of symptoms was 5.1 years. As shown by Table 1, 157 patients (60 per cent) presented

TABLE 1. *Duration of Symptoms in Patients Without Complications.*

DURATION	NO. OF CASES	PERCENTAGE
yr.		
Less than 1	39	25
1–2	34	22
3–4	23	15
5–9	30	19
10 or more	23	15
Unknown	8	5
Total	157	

at operation no biliary disease other than gallstones. Their histories reveal that symptoms were present for as long as thirty-nine years, with the average period 4.6 years. It is significant that 34 per cent of the patients had symptoms for more than five years and 15 per cent for more than ten years.

One hundred and three patients (40 per cent) had one or more complications at operation, including acute cholecystitis, acute pancreatitis, choledocholithiasis and carcinoma of the gall bladder (Table 2); of these, 6 had more than one complica-

TABLE 2. *Duration of Symptoms in Patients With Complications.*

DURATION	NO. OF CASES	PERCENTAGE
yr.		
Less than 1	36	33
1–2	15	14
3–4	38	35
5–9	17	15
10 or more	3	3
Total	109*	

*6 patients listed twice, having had more than one complication.

tion and are therefore listed twice. Whereas the average duration in the cases without complications was 4.6 years, it was 6.7 years in the cases with complications. Generally speaking, the longer the duration of symptoms of gallstones, the greater was the probability of complications. The interesting fact is that of this series 33 per cent had symptoms for less than one year before operation and 47 per cent for less than three years.

Sixty-nine patients (27 per cent) had acute cholecystitis, including empyema, gangrene and acute free perforation of the gall bladder (Table 3). The

TABLE 3. *Duration of Symptoms in Patients with Acute Cholecystitis.*

DURATION	NO. OF CASES	PERCENTAGE
yr.		
Less than 1	23	33
1–2	8	12
3–4	12	17
5 or more	24	35
Unknown	2	3
Total	69	

average duration of symptoms was 4.9 years, which is practically the same interval as in the cases without complications. Although 35 per cent of the patients were operated on after having had symptoms for five or more years, 33 per cent had had symptoms for less than one year. Six had no symptoms before the acute attack precipitating operation. These figures correspond with those in an analysis by Glenn,[7] according to which 7 per cent of a series of patients had complications at the time of the initial symptoms and approximately 40 per cent had had symptoms for less than one year. It is thus apparent that acute cholecystitis may develop either early or late during the course of gallstones.

Although there is no general agreement concerning the pathogenesis of acute pancreatitis, a significant and fairly constant finding is its association with gallstones.[8] Calculi have been reported in 70 to 81 per cent of cases of acute pancreatitis,[9] which is therefore usually considered a complication of gallstones. In the present series 10 patients (4 per cent) had acute pancreatitis (Table 4). These cases,

TABLE 4. *Duration of Symptoms in Patients with Acute Pancreatitis.*

DURATION	NO. OF CASES	PERCENTAGE
yr.		
Less than 1	5	50
1–2	3	30
10 or more	2	20
Total	10	

according to Abell's[10] classification, included acute pancreatic edema, acute pancreatic necrosis and acute pancreatic necrosis with hemorrhage. Five patients in this group had symptoms for less than one year before operation, 2 having acute pancreatitis with their first attack of biliary distress; 3 had symptoms for two years and 2 for thirteen and seventeen years, respectively. The average duration was 3.9 years. Acute pancreatitis was oftener an early complication than a late sequela of gallstones.

Thirty-two patients (12 per cent) had stones in the common duct (Table 5). The average duration

TABLE 5. *Duration of Symptoms in Patients with Choledocholithiasis.*

DURATION	NO. OF CASES	PERCENTAGE
yr.		
Less than 1	10	31
1–2	4	12
3–9	13	41
10 or more	5	16
Total	32	

of symptoms was 5.6 years, which with the exception of the cases of carcinoma of the gall bladder was the longest for those with complications. The duration period varied from less than one year to twenty years, except for 1 case with symptoms for forty years. Ten patients (31 per cent) were operated on before the end of twelve months; in fact, 3 were found to have stones in the common duct at operation following the first attack of colic. Fifty

seven per cent, however, had had symptoms for three or more years. The incidence of stones in the common duct relative to the duration of symptoms seems to be a subject of disagreement among authors. Heyd[11] reports the frequency of such stones as ranging from 1.9 per cent of patients with symptoms for less than two years to 16 per cent of those with symptoms from ten to thirty-five years, whereas Lahey and Swinton[12] report that 46 per cent of patients with common-duct stones have had symptoms for less than one year.

It is generally accepted that gallstones predispose to malignant change in the biliary tract.[13,14] They are found in most cases of carcinoma of the gall bladder,[15] and considerable evidence has been presented that stones precede biliary carcinoma.[16] On the other hand, the usual incidence of carcinoma of the gall bladder in cholelithiasis is only 0.5 to 1.5 per cent,[17] although it has been pointed out that its frequency is probably low because many patients undergo early cholecystectomy.[11,13,14] Of 3 patients (1 per cent) in the present series with carcinoma of the gall bladder, 2 also had choledocholithiasis. Symptoms had been present for six, twenty-seven and forty years respectively, — an average of twenty-four years. Although carcinoma has been reported when symptoms were of short duration,[18] most reports state that they were present for ten or more years.[13,16,19] Its rarity as a complication of gallstones[14] discounts it as a real risk in the temporary postponement of cholecystectomy.

In cases of long-standing gallstones, scarring, thickening and deformity of the liver edge are considered by some investigators as evidence of localized hepatitis,[20] whereas others think that the gross appearance of the liver is of little prognostic value.[21] Livers that look damaged, it is stated, frequently show no appreciable evidence of parenchymal change. The liver has been shown to have a tremendous reserve power,[22] and many hepatic functions are maintained even when only 20 per cent of the total liver tissue is normal.[23] Risk of operation because of liver damage can usually be combated and minimized by adequate preoperative management, and the optimum time of operation can be determined by appropriate liver-function tests.

Whether gallstones are a factor in diabetes or whether there is a metabolic process common to both is unsettled. Gallstones do appear to develop more frequently in patients with diabetes than in the population at large,[14] and complications of gallstones seem to be more frequent in diabetic patients than in nondiabetic.[24] Six patients in the present series had diabetes in addition to gallstones. The average duration of symptoms before operation was almost ten years. One also had acute cholecystitis, and another had a combination of acute cholecystitis, acute pancreatitis and stones in the common duct. Delay in surgery in diabetic cases apparently does not effect the course of the diabetes. At the George F. Baker Clinic in Boston, it has been found that diabetic patients require as much insulin after cholecystectomy as before.[24]

Conclusions

It is evident from this study that the sequelae of cholelithiasis do not appear at any well-defined time interval after the presence of stones is first determined. Biliary complications may be present with the initial attack or appear shortly after calculi are first demonstrated. On the other hand, complications may not develop for many years after cholelithiasis has been diagnosed or may never occur in spite of recurring attacks of biliary colic over many years. Yet in general it can be accepted that the longer symptoms continue in cholelithiasis, the greater is the possibility of biliary complications. The likelihood of the development of complications in any person known to harbor gallstones must be constantly borne in mind.

Biliary calculi should be removed, if practicable, as soon as possible after their presence is known. Today, however, because of wartime exigencies and the shortage of medical and hospital personnel, any elective operation such as cholecystectomy for gallstones without complications may have to be deferred. Until operation can be arranged, every effort should be made to reduce the dangers inherent in delay. Patients who cannot be operated on promptly should be put on a strict regimen of diet and hygiene in an effort to lengthen the period between attacks. They should be warned of the dangers of biliary complications and the necessity of seeking prompt medical advice. Should patients develop acute biliary emergencies, — and perforation of the gall bladder may occur within twenty-four hours of the onset of acute cholecystitis, — hospital beds should be promptly available, even if it means that hospitals postpone the admission of patients scheduled for elective operations. If these safeguards are observed, it should be possible for the duration of the war to minimize the risks involved in the postponement of operation for gallstones.

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Discussion

Dr. I. S. Otis, Meriden, Connecticut: The pathologic state of the gall bladder cannot always be safely estimated by any physical or laboratory test, hence the danger of delay. Not infrequently the problem arises of persuading a patient to have surgery when he or she seems to have recovered. Such patients are courting certain trouble, and the necessity for operation should be insisted on at the first evidence of suggested symptoms. Here the attending physician is invaluable in leading the patient to such a decision.

According to Eliason and Stevens, there is liable to be serious biliary damage because of the long period of the disease existing before the acute attack precipitating the operation. Often pancreatitis and hepatitis, together with cardiac and renal disease, result in operative and postoperative deaths. It is odd that although surgeons are almost universally agreed that acute appendicitis should be treated surgically as an emergency, — within hours, not days, — in acute cholecystitis, in which it is generally agreed that one cannot foretell the severity of the pathologic condition, they sometimes wait an indefinite time before instituting surgery. This position seems doubly untenable when some writers report perforations as having occurred within twenty-four hours. Heuer, in an analysis of 35,000 cases, shows that 20 per cent progressed to perforation, with a mortality of 10 per cent. Others give frequencies of perforation up to 45 per cent. MacDonald in 1941 pointed out that gall-bladder disease in its early stages is often viewed with "alarming nonchalance". It is this very attitude that may be responsible for the frequently disappointing results following belated operation. Graham illustrates the danger of procrastination by citing the mortality rates for cholecystectomy. After two attacks it is 2 to 3 per cent, after three or more attacks 8 to 9 per cent, in the presence of jaundice 10 to 12 per cent, and with pancreatitis 50 per cent.

In Dr. Bearse's series, it is to be noted that 103 patients (40 per cent) had one or more complications at operation, with an average duration only two years greater than that in the cases without complications. Add to this fact that 33 per cent had symptoms for less than one year and 47 per cent for less than three years, and one sees that the principle of exercising the best surgical judgment should remain firm. Despite the pleas of patients concerning the lack of domestic help to care for children, as well as the desire of workers to remain constantly on their jobs, they should not be permitted to alter the surgeons' primary desire to reduce mortality and morbidity. The latter should continue to advise early surgery. It is equally the responsibility of the medical profession to bend every effort toward the provision of prompt hospital facilities. Acute cases should not be refused admission even if such admission requires the taking over of ward beds and the release of beds earmarked for elective treatment. In this age, when so much progress is being made in medicine and surgery, every effort should be made by surgeons in the furtherance and encouragement of such a program despite the economic situation as it exists. The economic plea for delay means complications involving not only a greater mortality rate but also greater morbidity and economic loss.

Dr. John Fallon, Worcester: No paper could be more timely than this. When lifeboats are crowded we acknowledge the law of the sea. Now hospitals are crowded and we have another law: "The sickest first." The eleventh-hour patient, if compellingly sick, must come before him who has borne the aggravations of the waiting list. Otherwise hospitals are only hotels and we are hazarding a life to keep a promise.

One of the operations we can usually delay is cholecystectomy. But when and for how long? Cholecystitis without stone can be delayed to the end of the war or, so far as I am concerned, the end of the next war. On the other hand, jaundice or a suspicion of peritoneal inflammation demands hospitalization. Between these two extremes where do we stand? The man with attacks increasing in strength, frequency or length is lucky. He has a stone lodged in the pelvis or cystic duct, and empyema, perforation or progress into the common duct are in the offing. Still, he is lucky because he has been warned. He can beat the storm. The others, those with colics every rainy Tuesday, can wait a little. The law of averages is with them, although Dr. Bearse shows that a considerable minority have serious complications within a year of diagnosis, and I remember at least two deaths in the first attack. In other words, the law of averages says we can wait a little, but we have no data concerning how long "a little" is.

If we cannot say how long to delay, we can say how much harm delay does. Of a group of 1000 Fallon Clinic patients whose chief lesion was nonmalignant disease of the gall bladder or ducts, 41 died. Note that we are considering not the risk of operation but the risk of the disease. The series, to be fair, includes the 76 patients whom we tried to tide over without operation or until a more hopeful time for operation.

Seven of these 41 deaths may be called accidents. These were the overwhelming attacks coming, without reasonable warning, in the old and decrepit and the emboli and coronary occlusions. Fifteen deaths were the fault of a doctor, — oftenest myself, — shock, pneumonia (which is decreasing since the use of spinal anesthesia) or plain bad surgery done by someone before us or by one of us. But the majority, 19, were due to delay, despite adequate warning, until there were touch-and-go complications. It will be said that some of these deaths might have been saved by better judgment or better technic. True, but if there had been no delay, miracles would not have been needed. And the argument is academic when the mortality of operation for uncomplicated disease is a small fraction of 1 per cent.

Fundamentally, delay killed these 19 patients just as it contributed toward the deaths of several others and, among living and dead, added up a sum of misery not reducible to figures.

How long can we delay? Certainly long enough to give priority to the acute patient but not to a patient with a hernia that can be controlled by truss. Who knows where the fuse is set on a time bomb? If that bomb is buried under your own liver, delay takes courage. I should have to wait longer nowadays, but when I found out several years ago that I had gallstones, I delayed just one day, and only because the day was Christmas. When I tell my patients that story they say, "Ah, but you went to a good surgeon."

LOW-BACK PAIN AS THE PRESENTING SYMPTOM OF MALIGNANT BREAST TUMORS

MAJOR THEODORE D. COHN, M.C., AND CAPTAIN HAROLD COHN, M.C.

PRIMARY malignant tumors of the female breast that have metastasized to the vertebral column and bony pelvis are not infrequently overlooked. These patients are at times erroneously treated for the numerous other causes of backache, such as "lumbago," "sciatica," sacroiliac strain and retroversion of the uterus. The frequency of diffuse skeletal metastases from relatively small malignant nodules in the breast is a well-recognized clinical fact, but the subject has not been extensively discussed or become crystallized in the literature.

Lamarque[1] in his discussion of sketetal metastases from breast cancer makes the point that many of his patients complained of vague bone pains or suffered from pathologic fracture before a small tumor, until then unrecognized, was discovered in the breast. Ducuing[2] maintains that the invasion of the skeleton may present the first symptoms of a breast cancer, which are frequently ignored. This can be manifested by a bony tumor, pains in the bones or spontaneous fracture. The initial cancer may pass unnoticed either because of its small size or because of large breasts that mask the tumor, the breast tumor then revealing itself late. Warren and Witham[3] state that the first symptoms noted in malignant tumors of the breast are at times due to metastases, such as pathologic fracture or evidence of intracranial pressure. The prime purpose of this paper is not only to reiterate and emphasize that spinal metastases from an unrecognized breast tumor may be the cause of chronic low-back pain and may cause the presenting symptoms, but also to discuss the significance of such metastatic patterns in the light of new knowledge.

CASE REPORTS

CASE 1. A 52-year-old woman complained of low-back pain of 3 months' duration. She had been treated for a sacroiliac strain and myofibrositis of the lumbar muscles, with diathermy and local heat.

Physical examination revealed a well-nourished, middle-aged woman with negative physical findings except for a nodule in the middle of the right border of the right breast. The breasts were somewhat large and pendulous. A lymph node in the axilla was palpable. Biopsy revealed a scirrhous carcinoma of the breast. X-ray examination of the spine showed involvement of the 4th and 5th lumbar vertebras and some infiltration in the body of the ilium.

The diagnosis was carcinoma of the breast with metastases to the spine.

CASE 2. A 50-year-old woman had been treated for low-back pain with diathermy and local heat for 1 month prior to her present illness. She was wearing a sacroiliac belt. A nodule the size of a walnut was found above the nipple in the right breast. Biopsy proved this to be a scirrhous carcinoma, and roentgenologic study of the spine revealed the lesions of bony metastases involving the sacroiliac joint and the lower lumbar vertebras.

CASE 3. A 31-year-old woman underwent a ventral uterine suspension for low-back pain 3 years prior to her present illness. One year after the operation a nodule was found in the left breast; it was pronounced clinically nonmalignant and a diagnosis of cystic mastitis was made. She became pregnant and delivered a normal child. Three months post partum, while bending down to pick up her baby, she felt a sudden "crack" in the back and could not stand up.

A physician made a diagnosis of sacroiliac strain and strapped the back. The condition grew steadily worse, and the pain developed a left sciatic distribution. X-ray examination of the spine was negative. The patient was treated with short-wave therapy, strapping and a sacroiliac belt, obtaining only transient relief. Two months later, it was found that there was some degree of anesthesia over the left anal fold, as well as loss of the left Achilles reflex. A tentative diagnosis of cauda-equina tumor or herniation of a nucleus pulposus was made. Lipiodol studies of the spine were negative.

Throughout this period no attention was paid to the breast. The pain became severer and a back brace was ordered, with little relief. Subsequent examination revealed the breast mass to be the size of a hen's egg; it was hard and adherent to the skin. An enlarged node was found in the axilla. A diagnosis of carcinoma of the breast with bone metastases was made. Re-examination by x-ray, 4 months after the original films were taken, showed generalized spinal and pelvic metastases and some metastatic nodules in the skull.

The patient eventually died, and autopsy proved the lesion to be an adenocarcinoma of the breast with generalized spinal rib and skull metastases. The original x-ray films were reviewed but no demonstrable lesions were observed.

CASE 4. A 55-year-old woman complained of pain in the back of 5 months' duration. She had been treated for sacroiliac disease and low-back pain.

Physical examination showed tenderness over the left sacroiliac joint and pain in the left sciatic notch, with radiation down the left leg and over the right hip joint. A mass the size of a large hazel nut, adherent to the skin and nontender, was palpated in the right upper quadrant of the right breast. A few lymph nodes were palpated in the right axilla.

The diagnosis was carcinoma of the breast with spinal and pelvic metastases. This was confirmed by punch biopsy. X-ray study of the spine and pelvis showed metastatic involvement of the lumbar vertebras, left sacroiliac joint, left ischium and right hip.

DISCUSSION

It may seem elementary to suggest examination of the breasts in women suffering from back pain, but the 4 cases presented illustrate the importance of this procedure in all patients with complaints referable to the skeletal system. Such examination should be routine even if the patient is completely unaware of any mammary nodule or ulceration. As illustrated by Case 3, bone lesions may not become apparent roentgenologically until considerable bone tissue has been destroyed. Negative x-ray findings in the presence of bone pain and a nodule in the breast should not rule out bone metastases, at least early in the disease, and the patient should be followed by subsequent bone x-ray studies. Case 3 also illustrates the time-consuming, uncomfortable and extensive procedures that are often performed

before the true nature of the primary disease is recognized. This patient had lipiodol studies of the spinal canal, orthopedic appliances had been prescribed, and she had even been accused of hysteria.

* * *

Batson[4, 5] has described the probable route of metastases from the breast. According to this concept there is a vast intercommunicating system of veins between the epidural and vertebral veins and the veins of the thoracicoabdominal cavity. This system of veins has no valves and the venous pressure is extremely low. With every increase of intra-abdominal and intrathoracic pressure, the intratruncal pressure is raised to sufficient heights to permit the blood to flow into this vertebral system of veins. Thus there is a reversal of blood flow that bypasses the cardiopulmonary circuit. Since this system has no valves, a flow of blood occurs up and down the spine and into the skull. It does not involve the heart and lungs, and has many connections with the thoracicoabdominal system of veins. According to Batson, this provides a ready vehicle for the explanation of aberrant metastatic patterns and removes the stumbling block of the absence of lung involvement. The course through a patent foramen ovale, he states, is no longer necessary to explain this lung paradox. This system of vertebral veins is also called the meningoarachnoid system.

By means of injections of radio-opaque dyes and subsequent roentgenography, as well as post-mortem intravenous injection of the mammary veins, Batson has demonstrated the role of these veins in spinal metastases from malignant tumors of the breast. He has shown that this vast vertebral plexus is constantly the site of a physiologic reversal of blood flow and communicates with the veins of the spinal column as well as those of the breast. Thus the spine may be the site of metastases from breast tumors long before the original lesion has been recognized. Batson writes:

> According to this concept, in every act of straining, coughing or lifting with the upper extremity, blood is not only prevented from entering the thoracicoabdominal cavity; it is actually squeezed out of the cavity. Tumors and abscesses of the thoracicoabdominal wall, including the breast, tumors of the lung, pelvic tumors and abscesses, lesions of the shoulder and pelvic girdles and occasionally tumors and abscesses of other organs have connections with this vein system and may therefore have metastases distributed anywhere along the system without involving the portal, pulmonary or caval systems.

Batson experimentally demonstrated the spread of flow from the caval system into the vertebral system by increasing the intra-abdominal pressure in monkeys. He applied a tight binder over the animal's abdomen, and by increasing the pressure of the binder succeeded in shunting the flow into the vertebral system. This observation might be clinically applied to these metastatic bone patterns. The tight girdles that women frequently wear may increase the intratruncal pressure sufficiently to cause this paradoxical flow into the vertebral veins.

These patients demonstrate clinically Batson's contention that metastases to the spine do occur directly via the vertebral veins. Interestingly, all except Case 3 showed involvement of the lower spine and pelvis. Case 3 showed the diffuse type of bone metastasis. One might expect the other three patients to show more involvement of the shoulder girdle and upper spine, as Batson demonstrated with his injection experiments of the breast. One can explain this, however, on the basis of the flow in the valveless veins descending the spine. It might be noted in passing that since the vertebral veins richly anastomose with the thoracicoabdominal regions, other malignant neoplasms, such as pelvic and lung tumors, may also metastasize early to the spine. These may also show the picture of bone pain as the presenting symptom.

Summary

Four cases of carcinoma of the breast are presented in which pain from metastatic foci to the spine and bony pelvis was the first evidence of neoplastic disease.

Negative bone x-ray films early in the disease, in the presence of bone pain and a mass in the breast that has proved malignant, should not rule out bone metastases. X-ray studies should follow.

The probable route of metastasis by way of the vertebral veins, as described and suggested by Batson, is discussed.

Metastatic foci to the lower back and pelvis from a primary breast tumor should be considered as a not uncommon cause of low-back pain.

Breasts of all patients, especially women, should be examined routinely for tumors, particularly in the presence of low-back or pelvic pain.

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MEDICAL PROGRESS

INSECT VECTORS OF DISEASE (Continued)

VLADO A. GETTING, M.D., DR.P.H.*

CONENOSE BUGS

The conenose bugs belong to the order Hemiptera, family Reduviidae.[91] They are commonly called "assassin bugs," "kissing bugs," "corsairs," "black corsairs," "wheel bugs" and "bedbug hunters." Predatory in nature, several species protect themselves by biting, whereas others have developed a distinct habit of sucking mammalian blood. Two genera, Triatoma and Rhodius, contain conenose bugs of medical interest. Although a few species are worldwide in distribution, the majority are found in the Western Hemisphere, particularly in the high cold regions of the Andes.

Most conenose bugs are active runners and good fliers. Since white man's invasion of South America, these bugs have become domesticated and now can be found in the straw huts of Indians in Brazil. They live in the cracks of the more permanent structures, and live on man and domestic animals. Adults of both sexes bite; the larvae and nymphs are wingless and therefore restrict their activity to the house. Nocturnal in habit, they quickly run for shelter when suddenly exposed to light. The bite is usually painless,[92] so that a person bitten in his sleep is not awakened. The blood meal, lasting from a few minutes to half an hour, is followed by defecation of liquid feces. All the conenose bugs that bite man or animal infected with *Trypanosoma cruzi* become infected and retain the infection until death.[93] Although adult trypanosomes occur sparingly in the blood of patients with Chagas disease, nevertheless, when taken up by conenose-bug nymphs or adults, they lose their flagella and are transformed into "leishmania forms." In this stage, the trypanosomes multiply rapidly and develop into "crithidia," which in turn develop in the hindgut of the bug into the infective trypanosome forms. These infective forms then enter a new host (man or other vertebrate) through the medium of the infected feces deposited on the mucous membrane of the mouth or nose or on the conjunctiva of the eye or through the puncture wound created by the bug bite, an abrasion or an excoriation of the skin. Brumpt[94] proposed a method of diagnosis that calls for an insect vector (xenos) being fed on a suspected case, the bug being examined eight days later for the developmental stages of the trypanosomes.

Tryp. cruzi occurs naturally in armadillos, opossums, squirrels, certain monkeys, bats, cats, dogs and a California wood rat. *Triatoma gerstakeri* naturally infected with *Tryp. cruzi* were studied by Packchanian[95, 96] in southern Texas. Naturally infected triatoma have also been found in Arizona by Wood[97] and in California and Texas by Davis.[98] The nymphs of *Tr. gerstakeri* often occur in the nests of wood rats. *Tr. megista* is the most important vector of Chagas disease in the greater part of Brazil, and *Rhodnius prolixus*, primarily a human parasite, is the chief vector in northern South America.

The conenose bug is also incriminated as a mechanical vector of Western equine encephalomyelitis and of yellow fever.

The destruction of reduviid bugs is difficult as fumigation or insecticide spraying in tropical huts is impractical. Mosquito nets at night and adequate screening of houses offer protection against the adult bugs; however, the small nymphs are difficult to eliminate. Burning of infected huts may have to be performed as a last resort.

LICE

The order Anoplura, family Pediculidae, includes the sucking lice that subsist on blood. They attack man and other vertebrates and are vectors of typhus fever,[99] trench fever[85] European relapsing fever and, less frequently, plague. Urticaria and melanodermia (Vagabond's disease) may follow from the bite. Because of irritation produced by the bite, scratching may result in cutaneous pyogenic lesions. The head louse may transmit typhus fever, and is also accused of transmitting favus and impetigo. So far as is known, the pubic or crab louse is not a vector. The body louse is by far the most important vector. Man and his clothing are the chief disseminators of body lice. Whenever the temperature of the environment approaches that of the body, the louse leaves the vicinity of the body and wanders about in search of other hosts. Hence, under crowded conditions, where several human beings are huddled either in search of heat or shelter from enemy action, the louse is afforded ample opportunity for new infestations. Typically, lousiness and louse-borne diseases are cold-weather affairs. A temperature of 86 to 90°F. — that which exists between the skin and clothing — is ideal for lice. Eggs are attached to the fibers of clothing, especially woolens. Cotton and silk are less likely to harbor lice, owing to the lack of fiber. The eggs of the head louse are attached to the hairs covering the head, whereas the nits of the crab louse can be found on the pubic hair or on the hair of the eyebrows and the beard.

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Fleas

The order Siphonaptera contains the wingless, hard-bodied, small, brown, parasitic fleas, which are provided with powerful legs adapted for jumping.[65, 100] Adults of both sexes bite and suck blood; they are active and may jump upward 20 cm. or horizontally for almost twice that distance. Fleas leave the body of a dead host as soon as it begins to cool, seeking a new host. Often showing a preference for certain parts of the body, the adults are normally body parasites. The nests or dens, however, of animal and birds are normal breeding places. Fleas feed at frequent intervals, usually at least once a day, but occasionally much oftener since they are easily disturbed while feeding and seldom complete a meal. Even with a filled digestive tract, a flea may pass unaltered blood in the feces and still be feeding.

Fleas are important vectors of plague[101] and endemic typhus fever and mechanically transmit yellow fever. The ordinary rat flea *Xenopsylla cheopsis*, after feeding on an infected animal, may have its digestive tract full or even possibly blocked by solid growths of plague bacillus. Such fleas may regurgitate blood containing the plague bacillus into the wound, or may pass the organism into the feces, which in turn may be introduced into the skin either through the puncture or as a result of an abrasion.

Probably the smallest known flea is the jigger, sand flea or chigoe[102] (the chigger is not a flea but a larval mite[103]). This flea is an especially annoying pest in the tropics and subtropics, where it may occur in extremely large numbers, especially in dry dust and about human habitations. The female burrows into the skin, particularly beneath the toes, under toenails and in tender parts of the feet to lay eggs, and receives nourishment from the blood. The abdomen of the female flea begins to swell to the size of a pea, the posterior end barely reaches beyond the swelling of the host's skin and forms a plug for the hole. The eggs mature and are expelled through the tip of the abdomen, the female then shrivels up and drops out or is expelled by ulceration. Treatment of this flea is difficult and consists of aseptically removing the entire flea and consequent disinfection.

Ticks

Ticks are not true insects and belong to the class Arachnida, order Acarina.[104] The family Argasidae is comprised of soft ticks, while the family Ixodidae consists of hard ticks. Of the order Acarina, ticks are the most important transmitters of disease. They are now known to be vectors of relapsing fever (*Borrelia duttoni* type), Rocky Mountain spotted fever,[105] *fièvre boutonneuse*, African tick fever, Sao Paulo fever, tularemia, Chagas disease, louping ill, Western equine encephalomyelitis,[106] and American Q fever,[107, 108] and they occasionally transmit yellow fever and Rift Valley fever. Ticks are also an important cause of anemia in domestic animals, a female tick ingesting a hundred times her weight in blood. Moreover, certain species cause tick paralysis through venom contained in the salivary secretions of the mature female at a particular time of her life before she drops from the host on whom she is feeding.[109] This paralysis is ascending in type and may cause death. In northwestern United States and British Columbia the common wood tick *Dermacentor andersoni* and in Australia *Ixodes holocylus* have, in several cases, been reported as causing paralysis, respectively, of man and also of animals, calves, sheep and dogs.

The soft ticks are less parasitic than the hard ticks. The nymphs and adults are rapid feeders and tend to remain in the habitat of their hosts. There are two medically important genera, Argas and Ornithodoros.[110] *Argas persica* (the fowl tick, miana bug, blue bug or abode tick) is worldwide in distribution and an important poultry parasite whose habits are similar to that of the bedbug. It has a long life-span, — over four years if unfed, — and is a vector of fowl spirochetosis. Of the Ornithodoros ticks, there are some thirty species feeding on birds, mammals and reptiles,[111] and one species has experimentally transmitted rickettsial infections. Living in nests and burrows or the homes of man, they feed rapidly and intermittently. Their bite is painful, leaving an itching wheal. Of the six known species in the United States, *Ornithodoros coriaceus*, known as *pajarcello* in the southwestern states and Mexico, is most venomous and feeds on cattle and deer. *O. talaje* is found in Minnesota, Wisconsin, New York, the southwestern states and Central America; it is a vector of relapsing fever and lives in the dust, cracks and crevices of walls of resthouses and huts. It feeds on birds and mammals including man.

The hard ticks are shorter lived than the soft. Their eggs are usually deposited on the ground; the larvae climb grass stalks to await small rodents and other suitable hosts. Nymphs and adults similarly await larger hosts, including man. *Dermacentor andersoni*, the western wood tick, is the most important vector of Rocky Mountain spotted fever and tularemia and also is capable of transmitting equine encephalomyelitis. A three-host tick, the larvae and nymph feed on small rodents, such as field mice and squirrels, the adults on larger animals, such as horses, cattle, sheep, wolves and rabbits. Man is an accidental host. *D. variabilis*, the common dog tick, is frequent in the eastern United States as far north as Cape Cod; it is a vector of tularemia and Rocky Mountain spotted fever,[112] and it has been used experimentally to transmit Western equine encephalomyelitis.[113] Several species of Ixodidae have been experimentally proved to be capable of transmitting these diseases. *Haemaphysalis leporis palustris*, a widely distributed rabbit

tick, transmits naturally both Rocky Mountain spotted fever and tularemia.[114]

All tick vectors transmit disease from adult to eggs, to larvae and hence to nymphs and adults of the next generation. This hereditary transmission of disease complicates the control of tick-borne diseases. Soft ticks are controlled by methods used against bedbugs. Hard ticks, especially *D. andersoni* and *D. variabilis*, are extremely difficult to control. Tick-proof clothing, examination of oneself and one's clothing after passing through tick-infested areas, avoidance of underbrush and of herding sheep through an infested field, picking off ticks with tweezers and burning over underbrush, with the elimination of small rodents, are some control measures that have proved of value. Immunization against Rocky Mountain spotted fever in persons who are likely to be exposed is available by a vaccine prepared by the United States Public Health Service.[115]

A tick infected with Rocky Mountain spotted fever is not infectious until some time after attachment to the new host. The rickettsias are reactivated after a period of one and three-fourths hours to two or more days. Similarly, tick bites early in the spring are not likely to result in infection whereas tick bites in the fall are much more dangerous.

Transmission of Disease by Insect Vector

Infection of Vector

The vector of a disease is primarily infected by biting a person or animal that is a blood carrier of the disease in question, whereby the insect ingests the blood containing the infecting organisms. In certain of the insect-borne diseases, such as Rocky Mountain spotted fever,[116] the infective agent is transmitted by the primary insect host through the egg stage to succeeding generations. Occasionally the infective agent is passed from one insect to another during copulation. One or more of these methods may prevail in the case of certain diseases. Usually, when the infective agent is passed from one generation to another in the vector, the disease is persistent or long lived. The infective agent is not fatal to the vector, and there is evidence that this interrelation of the infective agent and the primary insect-host is sufficient to propagate the disease without the intervention of another host. This apparent symbiosis or survival of the infective agent in the insect host, with its transmission to subsequent generations, indicates that the disease is an old or usual one of that insect and that the infection of man is accidental, the latter being a true secondary host and unnecessary for the continued existence of the disease. These conditions are illustrated by the tick *D. andersoni* and the rickettsias of Rocky Mountain spotted fever.[117]

Infection of Host

The infective agent is transmitted usually to man or some other animal as a result of biting or attempted biting by the infected insect host. In some diseases the infected insect injects the organisms into the tissues of man in the act of biting; this is true in malaria; when the mosquito injects saliva into the tissue to maintain the blood fluid, malaria plasmodia are introduced into the victim. The regurgitation of stomach contents is occasionally the manner of infecting the bitten person; it is in this manner that fleas spread the bacteria of plague. In other instances, the surface of the skin is contaminated by the feces or glandular secretions of the infected insect, or by the infective material of an insect that is crushed on the skin as it bites. This infective material reaches the blood of the bitten person by being inoculated into the bite wound or through abrasions made by scratching or rubbing the bitten area. The infective agents of some of the insect-borne diseases, notably the bacteria of plague and the spirochetes of relapsing fever, can pass directly through the unbroken skin.

Biologic Transmission

Some of the organisms that cause insect-borne disease in men must undergo a stage of development in the body of the insect host before they can be transmitted to the human host. In such a disease both the insect host and man are necessary for the survival of the disease, and the absence of either results in the control or disappearance of the disease from the affected area. Control of this type of insect-borne disease is more feasible than that of the type in which the infective agent is passed through eggs from one generation of the insect host to the next.

Malaria and filariasis are examples of diseases that undergo this type of biologic development. The time required for the development of the parasite in the insect host constitutes the extrinsic period of incubation. The length of this extrinsic incubation varies for different organisms but is fairly constant for each organism, although influenced by temperature changes; colder weather lengthens the extrinsic period of incubation.

The life cycle of certain of the infective agents that undergo biological development includes a sexual and an asexual phase. The host in which the sexual phase occurs is called the "definitive host," whereas the one in which the asexual phase is passed is known as the "intermediate host." The insect vector or the human host may serve as a definitive or an intermediate host. In malaria, the sexual phase of the plasmodium occurs in the mosquito, which is the definitive host, and man is the intermediate host.[118] In filariasis, on the other hand, of which the infective agent is *Wuchereria bancrofti*,

man is the definitive host, and the mosquito the intermediate host.

An essential consideration in respect to biologic transmission is the appreciation that in some instances the infective agent undergoes a cyclic morphologic change in the body of the arthropod, whereas in others the parasite undergoes simple multiplication; in still others there is both a cyclic change and a multiplication. It is worth while to examine the different arthropods regarding these two characteristics. Epidemiologists are greatly concerned with these two factors because they affect so much the behavior and the geographic distribution of the disease concerned.[119] Both the interpretation of the observed epidemiologic phenomena and the institution of the indicated control measures are related to these characteristics.

The most complicated mechanism involved in biologic transmission of the infective agent is known as the cyclopropagative cycle. In this, the parasite undergoes a developmental cycle, with morphologic changes, and at the same time multiplies in the body of the insect host; both are entirely apart from any developmental process or multiplication taking place in man. The classic example of this cyclopropagative development is malaria. The sexual cycle, with multiplication, takes place in the mosquito, the definitive host[120]; and in man, the intermediate host, the plasmodium undergoes an asexual cycle. There are thus an extrinsic incubation period, during which the parasite undergoes change and increases in number in the mosquito, and an intrinsic incubation period, during which the asexual cycle takes place in man.

A second and less complete form of biologic transmission is the cyclodevelopmental cycle, in which the micro-organisms undergo a cyclic change in the arthropod host but do not multiply there. Here, the best example is filariasis, in which the worms undergo morphologic changes in the mosquito but do not increase in number. This disease, filariasis, was the first to be proved to be insect-borne, when Patrick Manson made his fundamental discovery in 1878.

The third type of biologic transmission is termed the propagative cycle, since the etiologic agent undergoes simple multiplication without morphologic changes. A typical example of this type of transmission is that of the rickettsias of typhus fever in lice.

Mechanical Transmission

When it is not necessary for the infective agent to undergo a period of development or multiplication in the arthropod host, biting vectors may transmit the disease mechanically. Usually, the infective agent spread by this means of transmission is a bacterium. The spread of bubonic plague or of typhoid fever is a good example of mechanical transmission.

It is evident that most of the important diseases of man with which epidemiologists are concerned fall into the group of diseases with biologic transmission. Those that undergo cyclopropagative and propagative transmission are of chief concern, since in these diseases the parasite undergoes multiplication and hence the survival of the parasite in the arthropod host is more certain and the infection of man is statistically likelier.

It is necessary to appreciate these facts in planning an attack on a disease suspected of being insect transmitted, for only in this way can the attack on the disease be logically and properly directed.

Prevalence of Insect-Borne Diseases

Within certain limits, the geographic distribution of an arthropod-borne disease is governed by the distribution and prevalence of the insect host. Consequently, an insect-borne disease can prevail only in districts where the insect hosts are indigenous and where environmental conditions are favorable for their continued existence. For example, yellow fever, which is spread by the *Aedes aegypti* mosquito, is a disease of the tropics, where that mosquito is indigenous. In the days of clipper ships, however, yellow fever outbreaks occurred in Boston. They usually started in the middle of summer and always disappeared with the first frost. The disease began near the wharves and spread in the direction of prevailing winds. Apparently what took place was that *A. aegypti* mosquitoes were brought north from the tropics by the clipper ships and then bred in the open barrels of water that were conveniently placed on the wharves as protection against fire. The mosquito continued to survive so long as environmental conditions were favorable, and the disease spread throughout the summer; but with the first frost the mosquito was killed and the outbreak subsided. Subsequent outbreaks were due to reimportation of infected mosquitoes.

Because the tropics and subtropics supply favorable conditions for mosquitoes, mosquito-borne diseases are prevalent in these regions. Conversely, louse-borne diseases occur most frequently in cold and temperate regions, since the conditions produced by cold, namely, the wearing of heavy clothing, crowding in houses for heat and inadequate personal hygiene, favor the propagation and dissemination of lice. This has been well illustrated by the occurrence of typhus fever in the concentration camps in Poland and in the armies on the Russian front.

Since no insect or arthropod is worldwide in distribution, no insect-borne disease is worldwide in distribution. Moreover, even if the insect vector is present, the insect-borne disease spread by that vector need not be prevalent. A classic example of this is the absence of yellow fever in Asia. For an insect-borne disease to prevail, the following conditions must exist: the vector must be indigenous or be able

TABLE 1. *Vectors of Arthropod-Borne Diseases modified from "Insects as Vectors of Virus Diseases," by James S. Simmons in* Virus and Rickettsial Diseases (*Cambridge: Harvard University Press, 1940*).

DISEASE	CLASS: ARACHNIDA						INSECTA								
	ORDER: ACARINA		ANOPLURA		HEMIPTERA		SIPHONAPTERA	DIPTERA							
	TICKS	HARVEST MITES	PARASITOID MITES	SUCKING LICE	BEDBUGS	CONENOSE BUGS	FLEAS	MOSQUITOES	SAND FLIES	GNATS	BUFFALO GNATS	GADFLIES	STABLE FLIES	TSETSE FLIES	FILTH FLIES
Helminths:															
Filariasis	—	—	—	—	—	—	—	x	—	x	—	x	—	—	—
Onchocerciasis	—	—	—	—	—	—	—	—	—	—	x	—	—	—	—
Protozoa:															
Malaria	—	—	—	—	—	—	—	x	—	—	—	—	—	—	—
Texas cattle fever	x	—	—	—	—	—	—	—	—	—	—	—	m	x	—
African sleeping sickness	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Chagas's disease	x	—	—	—	s	x	—	—	—	—	—	—	—	—	—
Leishmaniasis	—	—	—	—	s	—	—	s	?	—	—	—	—	—	—
Espundia	—	—	—	—	s	—	—	—	?	—	—	—	—	—	m
Bacteria:															
Enteric fevers	—	—	—	—	—	—	—	—	—	—	—	—	—	—	m
Plague	—	—	—	s	s	—	x	—	—	—	—	—	—	—	m
Tularemia	x	—	—	—	—	—	—	sm	—	—	—	x	—	—	m
Yaws	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Bartonellas:															
Oroya fever	—	—	—	—	—	—	—	—	x	—	—	—	—	—	—
Spirochetes:															
Relapsing fever (*B. duttoni* type)	x	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Relapsing fever (*B. recurrentis* type)	—	—	—	s	?	—	—	—	—	—	—	—	—	—	—
Rickettsias:															
Typhus fever (epidemic)	—	—	—	x	—	—	—	—	—	—	—	—	—	—	—
Typhus fever (endemic)	—	—	x	x	—	—	x	—	—	—	—	—	—	—	—
Trench fever	—	—	—	x	—	—	—	—	—	—	—	—	—	—	—
Rocky Mountain spotted fever	x	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Fièvre boutonneuse	x	—	—	—	—	—	—	—	—	—	—	—	—	—	—
African tick typhus	x	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Sao Paulo fever	x	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Tsutsugamushi fever	—	x	—	—	—	—	—	—	—	—	—	—	—	—	—
Viruses:															
Yellow fever	m	—	—	—	m	m	m	x	—	—	—	—	m	—	—
Dengue	—	—	—	—	—	—	—	x	—	—	—	—	—	—	—
Pappataci fever	—	—	—	—	—	—	—	—	x	—	—	—	—	—	—
Rift Valley fever?	s	—	—	—	—	—	—	s	—	—	—	—	—	—	—
Louping ill	x	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Equine encephalomyelitis	x	—	—	—	—	x	—	x	—	—	—	—	—	—	—
Epidemic encephalitis (Type B)	—	—	—	—	—	—	—	x	—	—	—	—	—	—	—
Epidemic encephalitis (St. Louis)?	—	—	—	—	—	—	—	s	—	—	—	—	—	—	—
Poliomyelitis?	—	—	—	—	s	—	—	—	—	—	—	—	m	—	—

x — usual method of transmission.
m — mechanical transmission.
s — survival of organisms.

to become indigenous; the vector must propagate under favorable environmental conditions; the vector must be present in sufficient numbers to spread and maintain an indigenous level of the disease (if the number of vectors is reduced to below this critical level, the disease cannot survive in epidemic proportions); susceptibles must be present and exposed to the vector; an infected person must be bitten by the vector, which must have access to the human host; environmental conditions must permit the vector to bite the infected host and then the to-be-infected host; and, finally, the vector must survive long enough to permit the parasite to undergo the extrinsic incubation period and then bite a new susceptible host. If any one of these conditions is unfavorable, the disease ceases to be epidemic and the cycle is broken; and if the cycle is broken often or long enough, the disease tends to disappear gradually from the area. If, on the other hand, one of the factors that was missing is replaced, the disease can be reintroduced or may assume epidemic proportions in an area where it was formerly endemic.

When the cycle of transmission includes an animal host of the parasite, the prevalence of the disease concerned is modified or entirely governed by the accessibility of the animal host. It is important to note that the survival of the disease and any plan to control it must take into consideration this additional factor. It is this type of disease, namely, animal-arthropod-man, that presents some of the most complicated and fascinating problems of epidemiology.

Classification of Insect-Borne Disease

Arthropods transmit not only diseases of man and other animals[121] but also diseases of insects and plants,[122] such as the diseases of the cabbage butterflies[123] and the various mosaic diseases of tobacco and tomatoes. So far as man is concerned, seven types of etiologic agents are transmitted by arthropods (Table 1). These are as follows: helminths (round worms); protozoa; bacteria; bartonellas; spirochetes; rickettsias; and viruses.

The helminths are transmitted only by Diptera — filariasis by mosquitoes, gnats and gadflies[124] and onchocerciasis by Buffalo gnats.

Among the protozoal diseases are malaria, spread by mosquitoes and the most devastating insect-borne disease in the world, Texas cattle fever, spread by ticks, African sleeping sickness, spread by tsetse flies, and Chagas's disease, spread by ticks and assassin bugs.

The most important insect-borne bacterial diseases are plague,[125, 126] spread by fleas, and tularemia, spread by ticks and gadflies.

Oroya fever, caused by a bartonella, is transmitted by sand flies.

The spirochetes of relapsing fever[127] are transmitted by ticks.

Of the rickettsial diseases, epidemic typhus fever is spread by lice and the endemic form by either lice, fleas or mites. Trench fever is also carried by lice. Rocky Mountain spotted fever,[128] *fièvre boutonneuse*, African tick typhus and Sao Paulo fever are transmitted by ticks, and Tsutsugamushi disease or scrub typhus is spread by harvest mites.

Of the insect-borne virus diseases, yellow fever, dengue,[129] equine encephalomyelitis[130] and possibly Japanese encephalitis[131] are transmitted by mosquitoes. Louping ill and equine encephalomyelitis are transmitted by ticks,[132, 133] but the latter is known to have been transmitted by the conenose or assassin bugs.

(To be concluded)

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

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CASE 31121

PRESENTATION OF CASE

A sixty-year-old married woman was admitted to the hospital complaining of abdominal pain, nausea and vomiting.

Seven years before admission, three months after repair of a cystocele, the patient first noticed a localized burning sensation in the back and pain under both costal margins, with morning nausea, vomiting and occasional diarrhea. This pain came in episodes that were intermittent until five years before admission, when the pain became persistent. A Graham test one year later revealed failure of filling and the presence of a gallstone in the gallbladder area. Three years before admission she had an acute attack of pain in the right upper quadrant, with nausea and vomiting. Since that time she had had frequent morning headaches and mild upper abdominal pain, which were relieved by vomiting. During the previous two years she had also had mild lower abdominal pains that were relieved by episodes of diarrhea. About a month before admission a barium enema in the Out Patient Department showed a transient delay in filling at the hepatic flexure, and a smooth, round, filling defect was seen projecting into the lumen of the transverse colon (Fig. 1). Barium later passed around this defect to the cecum and it was possible to outline a smooth ovoid mass, measuring about 9 by 5 cm. On palpation or contraction of the bowel the mass moved distally, and on a post-evacuation film it reached the midtransverse colon. With this movement of the mass the ascending colon became shortened. These findings were confirmed by a second barium enema.

Physical examination revealed an obese, well-developed woman. Examination of the heart and lungs was negative. The abdomen was moderately tender in the suprapubic area; there was no spasm. The liver and spleen were not felt, and no masses were palpated. Peristalsis was high pitched and hyperactive. A pelvic examination was not remarkable. A rectal examination revealed brown feces.

The temperature, pulse and respirations were normal. The blood pressure was 190 systolic, 120 diastolic.

The serum nonprotein nitrogen, protein and chloride were normal. Examination of the urine was negative. The white-cell count was 4100, and the hemoglobin 80 per cent. An oral Graham test was positive.

On the sixth hospital day an operation was performed.

DIFFERENTIAL DIAGNOSIS

DR. FRANCIS D. MOORE: At the age of fifty-three this patient began to have gastrointestinal symptoms that were compatible with, although not typical of, gall-bladder disease. One year later a gallstone was shown to be present, and this was undoubtedly regarded as the cause of her symptoms. At the age of fifty-eight, two years before she came to the hospital, a new set of symptoms arose, which evidently had to do with the other end of the gastrointestinal tract, since the pain was in the lower abdomen and associated with diarrhea. It is true that she had had some diarrhea with her supposed gallbladder attacks, but it apparently was not prominent. The new symptoms, however, were often relieved by the diarrhea, a train of events that strongly suggests an intermittently obstructing lesion.

Physical examination does not give us many clues but it does mention that the patient was obese and well developed, findings that one would not expect if she had had any sort of malignant tumor for either the two-year period or the seven-year period, accompanied respectively by the upper and lower gastro-

*On leave of absence.

intestinal symptoms. Peristalsis was referred to as high-pitched and hyperactive which is suggestive of obstruction, but without a more elaborate description it does not really establish the diagnosis. Obstruction is often associated with tinkling, hollow, peristaltic sounds whose occurrence is synchronous with crampy pain.

The patient had normal-colored feces, and no guaiac test is recorded. The white-cell count was normal, which suggests that infection or necrosis of the bowel was not a part of the picture. This impression is borne out by other vital signs.

FIGURE 1. *Roentgenogram after Barium Enema Showing Tumor Mass Advanced into Transverse Colon Pulling the Cecum after It.*

Now we come to the x-ray films, and I am sure that they will either make or break the diagnosis. Unfortunately no roentgenologist is present, so we shall have to rely on our own interpretation of the films.

There is a sausage-shaped mass in the right-hand portion of the transverse colon, which apparently advances at times over toward the splenic flexure. When it is in that position, the cecum is shortened and the terminal ileum is no longer visible. I do not see how one can avoid the diagnosis of intussusception in the presence of such findings. Only one of the many spot films, however, shows the characteristic dimple in the advancing end of the intussusception, and we have already noted the lack of evidence of inflammatory reaction or bowel necrosis, the presence of which would lead one to conclude that, if she had an intussusception, it was not affecting the blood supply of the bowel.

So the problem becomes one of trying to discover why this patient had an intussusception at the age of sixty and, secondarily, why this intussusception did not do her any more harm than it did.

I have recently seen a patient who had a sigmoidal intussusception presenting at the anus in which the blood supply of the intussuscepted bowel was still intact. The leading point of this intussusception was a large carcinoma, and there was considerable bleeding. From that patient one might conclude that it is at least possible for adults to have chronic intussusception that does not produce bowel necrosis, and such must be the case with the patient under discussion.

Another question to be answered is, What was the leading point of the intussusception? I have already mentioned that the x-ray films show a sausage-shaped mass without the characteristic dimple in the leading portion. This suggests that this portion is not the bowel wall itself but a fairly large mucosal or intramural tumor. If this were the case, it would

account for the lack of x-ray dimple and it might also suggest that, although the leading point was in the midtransverse colon, the actual amount of intussuscepted bowel was only a matter of a few centimeters above the ileocecal valve. The latter would make us feel more comfortable about the lack of evidence of bowel necrosis.

Such a smooth tumor could be a lipoma, fibroma, neurofibroma or lymphoma of the bowel wall. It would have to be in the terminal ileum or right at the ileocecal valve, because there is no evidence that the colon itself was being intussuscepted without pre-existing ileocecal intussusception.

Of these tumors, lymphoma is probably the most frequent, but lymphoma in the gastrointestinal tract tends to be multiple; even though occasional cases are recorded in which resection was curative, such cases are the exception. Furthermore, if this were lymphoma, I should expect that the patient would have had some bleeding from the region of the tumor itself.

I am therefore going to select a lipoma as the likeliest leading point for this intussusception. My diagnosis is intramural lipoma of the terminal ileum, with chronic ileocecal intussusception.

Possibly I am overlooking something in not trying to relate this lesion to the patient's antecedent gall-bladder disease. Although it is true that a gallstone might have ulcerated through into the colon, I can see no reason why it should not have passed down to the rectum; furthermore, one would not expect that its attempted passage down the bowel would have produced retraction and shortening of the cecum. This latter chain of events, it seems to me, can be produced by intussusception or attempted passage of a long pedunculated submucosal tumor and by nothing else.

Clinical Diagnoses

Polypoid tumor of the right colon, with intussusception.
Cholelithiasis.

Dr. Moore's Diagnoses

Submucosal pedunculated lipoma of the terminal ileum, with ileocecal intussusception.
Cholelithiasis.

Anatomical Diagnosis

Submucosal lipoma of ascending colon.

Pathological Discussion

Dr. Benjamin Castleman: At operation Dr. Allen carefully palpated the entire right colon and was unable to demonstrate the polyp that he had hoped to find. The bowel, however, had not been too well prepared. The bowel was not opened, and no resection was performed. There were dense inflammatory adhesions in the region of the gall bladder and the duodenum, and the hepatic flexure was slightly adherent to this region. A shriveled, chronically inflamed gall bladder, within which was a 1.5-cm. stone, was removed. The common duct was not explored.

The patient left the hospital on the seventh postoperative day. Most of her symptoms were relieved for several months, but she still had occasional crampy abdominal pain to the right of the umbilicus.

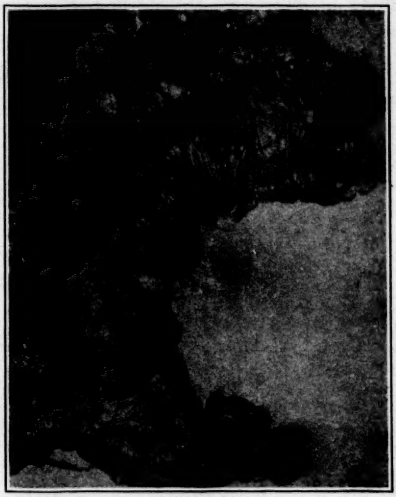

Figure 2.

Another barium enema still disclosed the polypoid lesion in the colon, and it was decided to operate again.

Once more Dr. Allen was unable to palpate a tumor in the ascending and transverse portions of the colon. Using a needle, air was carefully aspirated from the large bowel and the needle hole was then closed. When the right colon was mobilized, an extremely soft tumor could be felt in the ascending colon. About 18 cm. of the terminal ileum and the right colon was resected, and an ileotransverse colostomy was performed.

The tumor proved to be, as Dr. Moore predicted, a submucosal lipoma measuring 9 by 6 by 4 cm.; it was attached by a mucosal stalk 3.5 cm. in diameter at a point 10 cm. distal to the ileocecal valve (Fig. 2). The tumor was soft, malleable and easily compressible, which accounts for the great difficulty the surgeons had in palpating it through the serosal surface.

Will you comment on the x-ray films, Dr. Schulz?

Dr. Milford D. Schulz: This patient was examined on several occasions — twice prior to the

cholecystectomy and again after the operation. On all examinations a smooth-surfaced mass was seen in both the ascending and transverse colon. When it was in the transverse colon, the cecum was elevated as though the advancing tumor had pulled the cecum after it — an intussusception, with the tumor itself leading. This, as Dr. Moore has stated, accounts for the fact that the usual dimple in the intussusceptum was not seen. This dimple is more frequently seen in children, for then a tumor is seldom present, the leading part being the bowel itself; in adults, an absence of the dimple is almost the rule. That the tumor was soft and compressible is shown on the film of the contracted bowel, the tumor being much longer and narrower than the stated measurements. The appendix lay in the right upper quadrant below the liver, where it presumably had been drawn upward with the cecum when the tumor was advanced by peristalsis.

CASE 31122

Presentation of Case

First admission. A sixty-four-year-old Polish freight handler was admitted to the hospital with jaundice.

The patient was in good health until three weeks prior to admission, when he suddenly became nauseated and vomited some whitish material. The feeling of nausea lasted several hours, after which he felt better. A few days later the nausea recurred, accompanied by a "heavy feeling" in the epigastrium but no pain. He vomited several times, and his appetite became poor. Two weeks before entry, he noticed that his skin was becoming yellow. At the same time his stools became light colored and his urine dark. He stopped work and rested but did not improve. The heavy feeling in his epigastrium persisted as the jaundice increased, and he had two more attacks of vomiting. There was no itching, chills, fever or change in bowel habit. He lost about 8 pounds over a period of two weeks. During this same period he noted slight ankle edema, disappearing overnight.

The patient had had an attack of "double pneumonia" fifteen years prior to admission, following which he continued to have a chronic cough, which was worse in the morning and evening and productive of about 30 cc. of white sputum each day. He had never noted blood streaking or chest pain. About twelve years before entry, following severe trauma to the genitalia, the right scrotal sac had become swollen and acutely tender, after which it remained enlarged, without much alteration in size.

Physical examination on admission revealed a well-developed and well-nourished, deeply icteric man in no distress. The fingers were clubbed. There was bilateral marked arcus senilis, and the fundi showed moderate arteriovenous nicking. The chest was emphysematous, with poor motion, hyperresonance to percussion and diminished breath sounds and fremitus. Diffuse dry squeaks and rhonchi were heard, with sticky rales at the bases posteriorly. The heart sounds were distant. The liver was palpable three fingerbreadths below the costal margin, and the edge was smooth, sharp and nontender. The gall bladder could not be felt. The right scrotum contained a firm, 6-cm., nontender mass that failed to transmit light. A portion of the testis could be felt attached to the mass posteriorly.

The temperature was 99°F., the pulse 70, and the respirations 20. The blood pressure was 120 systolic, 70 diastolic.

Examination of the blood revealed a red-cell count of 3,650,000, with 12 gm. of hemoglobin, and a white-cell count of 8000, with 78 per cent neutrophils. The smear revealed a hypochromic microcytic anemia with many target cells. The urine had a specific gravity of 1.020, with a ++ test for albumin and a +++ test for bile and with a positive test for urobilinogen in a dilution of 1:2. The sediment contained 10 to 15 white cells and an occasional coarsely granular cast per high-power field. The stools were clay-colored, soft and occasionally guaiac positive. The serum protein was 5.7 gm. per 100 cc. with an albumin-globulin ratio of 1.3. The van den Bergh was 15.2 mg. per 100 cc. direct and 26.2 mg. indirect. The prothrombin time was normal, and the cephalin flocculation test negative. A bromsulfalein test showed 100 per cent retention. A galactose tolerance test, employing the injection of 50 cc. of a 50 per cent solution of galactose intravenously, revealed a blood level of 12.4 mg. per 100 cc. after 60 minutes, and one of 8.1 mg. after 75 minutes. The serum nonprotein nitrogen was normal, and the chloride was 95 milliequiv. per liter. Agglutination tests with the patient's serum against *Proteus vulgaris* X19, XK and X2 and *Leptospira icterohaemorrhagiae* and *L. canicola* were negative. The Hinton test was negative.

A roentgenogram of the chest showed no evidence of active disease in the lungs. The right costophrenic sinus was obliterated, owing to old adhesions. The heart showed no definite enlargement. A gastrointestinal series was negative.

Duodenal drainage was productive of 20 cc. of whitish, translucent fluid in an hour. Half an hour after the injection of 40 cc. of a saturated solution of magnesium sulfate, another 20 cc. of similar fluid was obtained. A smear of the sediment revealed no sodium bilirubinate or cholesterol crystals, nor were any bile-stained leukocytes seen. Culture revealed abundant colonies of colon bacilli.

The patient was placed on a high-carbohydrate, high-protein, high-vitamin, low-fat diet and given bile salts (0.1 gm. Degalol, three times a day). An

exploratory laparotomy was performed on the ninth hospital day. The liver presented an unusual granular mottling and seemed edematous, suggesting some form of hepatitis rather than cirrhosis. The gall bladder was normal, readily compressible and no stones were present. The head of the pancreas was soft. The common bile duct was of normal size and appearance. No biopsy specimen was taken.

Following the operation the patient seemed to improve. The van den Bergh gradually fell to 5.8 mg. direct and 8.8 mg. indirect, the stools became light brown, but no urobilinogen was present in the urine. He was discharged on the forty-third hospital day, to be followed in the Out Patient Department.

Second admission (ten weeks later). Following discharge, the patient continued to improve for about a month. The jaundice became less noticeable but never disappeared, and he gained a few pounds. About six weeks prior to admission he began to feel weak, with attacks of pain in the right upper quadrant and epigastrium, which were often stabbing in character, and occasional nausea. His stools again became light colored. He developed some unsteadiness of gait. At about that time, the van den Bergh was 15.8 mg. direct, and the serum protein 6.31 gm. per 100 cc., with an albumin-globulin ratio of 0.83. The cephalin flocculation test was negative, and the urine contained no urobilinogen.

On readmission the patient appeared cachectic and still deeply icteric. The liver was four finger-breadths below the costal margin and slightly tender. There was evidence of a small amount of fluid in the abdomen, and minimal pitting edema of the ankles was present. The deep tendon reflexes were hypoactive in the upper and absent in the lower extremities. There was a questionable extensor plantar response on the left.

A roentgenogram of the chest revealed no definite change from the previous examination. A gastrointestinal series showed considerable curling of the esophagus but no definite varices. The liver was enlarged, and the spleen slightly enlarged. The stomach was slightly compressed by the liver and spleen and showed rather marked thickening of the mucosal folds.

The serum protein was 5.76 gm. per 100 cc., with an albumin-globulin ratio of 0.73. The van den Bergh was 12.4 mg. direct and 13.6 mg. indirect. The cephalin flocculation test on one occasion was ± after twenty-four and ++ after forty-eight hours, and on another occasion negative. The alkaline phosphatase was 34.8 units per 100 cc. The prothrombin time, serum nonprotein nitrogen and chloride were normal. The cholesterol ranged from 147 to 250 mg. per 100 cc. The blood Hinton and Wassermann tests were positive. Urine examination revealed a ++++ test for bile and numerous tyrosine crystals. Urine urobilinogen varied from negative to positive in a dilution of 1:16. Duodenal drainage revealed a few bile casts and bilirubin crystals but no bile. The stools were light brown and occasionally guaiac positive.

On the thirty-first hospital day a laparotomy was performed.

Differential Diagnosis

Dr. Earle M. Chapman: "The stools were clay colored, soft and occasionally guaiac positive." I should like to know how many stools were guaiac positive.

Dr. Benjamin Castleman: The first stool examination was guaiac negative; the second, positive; the thlrd, ++; the fourth, +; and the fifth, negative.

Dr. Chapman: That is an important contribution. It is interesting that this man had disease in the chest. The x-ray does not reveal it. Physical examination says that rales were present, and I think that rales are a sign of disease. This case I believe is the epitome of the diagnostic problem, because one is presented with laboratory evidence which at one and the same time indicates an obstructive process and a nonobstructive type of jaundice. Obviously the attending physicians were puzzled as to which it was, for the first time they made a great effort to prove that it was obstructive and later on that it was nonobstructive. On the first admission, they must have been convinced that it was obstructive because the evidence leans more on that side and the patient was explored. But still the surgeon failed to give them a diagnosis. I want to pause and say that a biopsy of the liver at the first exploration would have been helpful.

The next thing I want to point out is that the head of the pancreas was described as soft. It has always been my opinion that the head of the pancreas is hard and firm and that at operation the surgeon sometimes has difficulty distinguishing the normal head of the pancreas from carcinoma.

Following exploration the patient improved. That is revealing and throws the diagnosis over into the nonobstructive field. I am sure that was the thought when he left the hospital. He finally returned and seemed to go back into the obstructive category, because he was again explored.

In going through the steps of making a diagnosis, it is helpful to use Rich's[1] classification of jaundice. He distinguishes two major types, retention jaundice and regurgitation jaundice, the latter being the obstructive and the former the nonobstructive, based on the fundamental pathology of the process. In retention jaundice the bilirubin is increased in the plasma, and since all of it is not removed by the liver cells an indirect van den Bergh reaction results. With this increase in blood bilirubin the kidneys excrete an increased amount of urobilin. What causes this? Three groups of disorders increase

blood bilirubin. The first is the anoxemic group — pernicious anemia, transfusion reaction, hemolytic jaundice, paroxysmal hemoglobinemia, phenylhydrazine poisoning and other types of blood disease that produce hemolysis. The second group comprises febrile diseases, and the attending physicians thought of this because they looked for positive agglutination tests with *Leptospira icterohaemorrhagiae*, *L. canicola* and various strains of *Proteus vulgaris*. The third group is Hanot's cirrhosis of unknown cause.

Then we come to the regurgitation type. Here, the plasma gives a direct van den Bergh reaction because it contains bile that has backed up secondary to obstruction of the biliary tract, possibly with injury to the bile canaliculi. This may be due to three causes — necrosis of the liver cells, frank obstruction in the biliary system and catarrhal jaundice, cause undetermined. The necrosis of liver cells from toxic agents may cause jaundice of either kind or of both types together.

The patient was a Polish freight handler, and although he may have been a heavy drinker, there is no history of alcoholism, so we have no cause to think of alcoholic hepatitis with liver-cell necrosis.

Now let us go back and look at the laboratory evidence and fit it into this classification. The laboratory tests do not favor the retention type as well as the regurgitation type. In favor of the retention type are the target-cell anemia, the urobilinogen, the negative duodenal drainage and the high indirect van den Bergh. In favor of regurgitation jaundice are the bile in the urine in considerable amounts, the high phosphatase, which goes with liver damage and especially necrosis of liver cells, and the final duodenal drainage before operation, because the record clearly describes cholesterol crystals and bile casts but no bile. Obviously these laboratory data do not give us the answer.

What are the clinical facts, divorced from the laboratory data, that help us arrive at a diagnosis? He was a sixty-three-year-old man who had had a tumor of the testis, who was jaundiced and who had a big spleen and liver. He undoubtedly had necrosis of the liver cells, because we know that he improved after exploration. Then came pain over the liver, more jaundice, weight loss and the appearance of general weakening and certain reflex changes in the leg. He developed a positive Hinton test, and above all he had guaiac-positive stools. I am so glad to get complete data on that because it is an important observation and outweighs all the laboratory evidence that was presented. This man had blood in his stools. Where was that blood coming from? From the gastrointestinal tract? Or is it possible for the necrosis of the liver cells in the regurgitation type to be severe enough to cause a positive guaiac test in the stools? As for the positive Hinton test, I am going to dismiss syphilis. I know that we have seen positive Hinton tests in the presence of liver damage. I say that because two or three years ago I became interested in the subject and have a collection of 5 cases in which this was so, with no other evidence of syphilis to go with it.

We have excluded the first and second groups under the retention type of jaundice. I do not believe that it was a Hanot's type of cirrhosis because the appearance of the liver would have told us whether or not it was a hypertrophic biliary type. At the first exploration we are told that there was no obstruction. Yet I cannot escape the final conclusion that there was obstruction, that they found some sort of process that obstructed the biliary system and that a great deal of liver-cell necrosis was also present.

If I have to make a choice in the correct order I hardly know what to say. I believe that he had malignant disease, and my first choice is carcinoma. Where are we going to put it? He might have had metastases in the liver and in the spine causing peripheral nerve changes; it might have been primary in the testicle injured years before, or it might have been a primary tumor of the colon with metastases to the liver and somewhere along the common duct that caused obstruction. That is my first choice. My second choice is that he had that rare thing causing a positive guaiac test in the stools, a carcinoma localized in the duodenum around the ampulla of Vater. It could still be carcinoma of the pancreas, part of it involving the ampulla of Vater and head of the pancreas, and I am still supported in this by the positive guaiac test, and that is why I may reverse the order and put it down as my first choice. My third choice is a regurgitation-type necrosis of the liver, a severe form of the toxic group.

DR. CASTLEMAN: Your first choice is carcinoma involving the head of the pancreas?

DR. CHAPMAN: Yes, and the ampulla of Vater.

DR. CASTLEMAN: How do you explain the normal common duct at operation?

DR. CHAPMAN: One other thing I meant to bring out was the matter of the common-duct drainage. The first time it is described the sediment revealed no sodium bilirubinate, cholesterol crystals or bile-stained leukocytes. I think it was Bockus[2] who found that most patients with silent stone in the common duct show evidence by drainage of either bilirubin crystals or bile-stained crystals. In the last drainage, no bile was seen but there were a few bile casts and bilirubin crystals. Possibly, a silent stone jammed down toward the ampulla should be my fourth choice.

DR. CASTLEMAN: You still have to assume that the common bile duct was distended.

DR. CHAPMAN: But the patient did not have complete obstruction. Obviously he had intermittent

obstruction because he was well after the first operation. Manipulation and pressure may have forced drainage around it.

DR. WILLIAM W. BECKMAN: I was impressed at the time of admission, before the laboratory work was done, by the fact that he stated that one day he was completely well and the next day he was sick and started to vomit. After a week he noticed jaundice. This seemed to me to be in favor of hepatitis of some sort. The laboratory data did not seem to support that diagnosis. Finally, an exploration was performed and I was delighted that my original idea was supported. I thought that he certainly had hepatitis but could not understand why he did not get better after two months. He was readmitted and there was a great deal of controversy, but we finally decided to re-explore.

DR. JACOB LERMAN: There are always differences of opinion about some clinical points. I saw this man in the Out Patient Department. A routine follow-up note said that he was better. I was quite sure that he was not, because the jaundice was just as severe, although the color of the skin had changed. It turned brown rather than green. I thought that his jaundice was complete and persistent and had not changed much since his stay in the hospital. The stools were noted as occasionally clay colored but usually brown. We checked that by doing bile determination on the brown stools and found that they did not contain any bile. Consequently the chances are that they were always equivalent to clay-colored stools.

DR. CHAPMAN: How did you know they were brown?

DR. LERMAN: They looked brown to the examiner and to the patient.

DR. CHESTER M. JONES: I saw the patient toward the end of his stay on the first admission and later on in the second admission. My feeling was much like that of Dr. Beckman, — that he had an acute episode of damage to the liver which might well have been on an infectious basis, — and I thought he ought to be treated for liver failure rather than anything else.

I remember seeing the first specimen of duodenal contents, and there is little reason to believe that the interpretation of the sediment was incorrect. There was no evidence of bile pigment, bile casts or crystals. In other words, no bile was obtained. I do not know about the second drainage. When I first saw this man I thought the picture was that of infection and I did say that there might be an intrahepatic block due to the type of infection that goes with infection of the common duct — cholangitis. Dr. Wallace's description at the time of the first operation was entirely consistent with a biliary type of obstruction that had not arrived at cirrhosis but presented a smooth, finely granular liver, with mottled discoloration.

The second time I saw him I still thought he had primary intrahepatic disease and that such was going to be found. If the biopsy at that time showed a biliary type of involvement, one had a right to explore the common duct again to see if there was any local tumor or other obstruction, such as a gallstone.

About the positive guaiac in the stool, the presence of occult blood can be found in any type of jaundice, regardless of its nature. It is found commonly if the jaundice is severe and of long standing. I think that it is not of diagnostic significance. In a group of seriously jaundiced patients there was a positive guaiac test in at least 40 or 50 per cent. This finding of occult blood is probably due to the fact that there is a tendency to spontaneous bleeding associated with a lack of prothrombin.

DR. FLETCHER H. COLBY: Did I understand that you seriously considered tumor of the testicle as the primary focus, with metastasis in the liver, as well as somewhere in the common duct and spine to explain the reflex changes? Would it not be unusual to have tumor for twelve years and not to have it metastasize before this? He was operated on and the surgeon found no demonstrable disease in the region of the gall bladder. We had one somewhat similar patient at the Huntington Hospital who, nine years before, had been given heavy external radiation. The only symptom of recurrence that this man had was jaundice. He was operated on with a diagnosis of possible gall-bladder disease, and he had a huge mass pressing on the common duct, a metastasis from the testicular tumor.

DR. JONES: Infiltration of the liver would not cause this picture.

CLINICAL DIAGNOSIS

Carcinoma of hepatic ducts.

DR. CHAPMAN'S DIAGNOSIS

Malignant disease: (?) carcinoma of head of pancreas, involving ampulla of Vater, (?) carcinoma of colon, with metastases to spine, liver and about common duct, (?) carcinoma, metastatic, to liver and about common duct from testicular tumor.

Common-duct stone?

ANATOMICAL DIAGNOSES

Adenocarcinoma of hepatic ducts, with metastases to pancreas.

Cirrhosis of liver, obstructive type, with acute hepatitis.

Bronchiectasis.

Cyst of pancreas.

PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: Dr. Wallace operated on this man after a peritoneoscopic biopsy had been done.

Peritoneoscopy showed severe bile stasis, biliary cirrhosis and marked dilatation of the bile ducts. We found a bile duct measuring 2 or 3 mm. in diameter in the biopsy specimen, which must have been taken from the periphery of the liver, so that this patient really had a hydrohepatosis. There was definite bile-duct proliferation (Fig. 1). Following this procedure, Dr. Wallace operated. He might tell us what he found.

DR. RICHARD H. WALLACE: I explored this patient on both occasions. I was much interested the first time because two days before I had operated on a woman with painless jaundice and removed a common-duct stone. This is especially noteworthy because of the relative infrequency of painless jaundice with common-duct stone. In the series

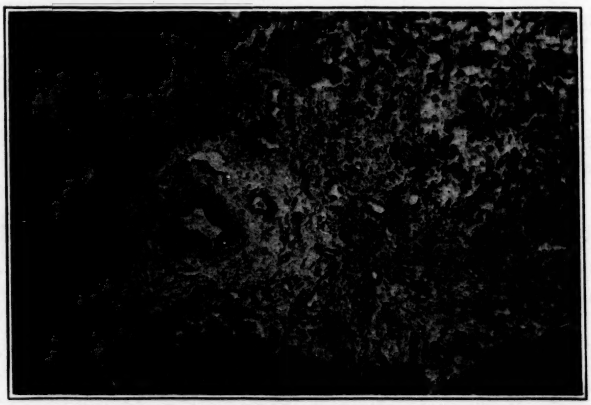

FIGURE 1. *Photomicrograph of Liver.*

that Dr. Allen and I[3] reviewed less than 2 per cent of the patients with common-duct stones were without pain.

At the first exploration, I found a normal gall bladder, a normal common duct and a normal pancreas, and except for the abnormal liver findings, the exploration was entirely negative. Following the biopsy of the liver by Dr. Benedict it was brought out that possibly there was a common-duct stone without a dilated common duct, which I had never seen. We rather hoped that we might find this at the second exploration. At that time, the gall bladder was still collapsed and on aspiration perfectly clear white mucoid material was obtained. The common duct was normal, the liver was smooth, bile stained and firm, and at the hilus of the liver there was a hard nodular mass that was not present at the first exploration. During the six-month interval between explorations it had grown down to involve the hepatic ducts, the extrahepatic ducts, the cystic duct and the ampulla of the gall bladder.

DR. CASTLEMAN: The patient died following the operation, and at autopsy we found a tumor involving both hepatic ducts. It had apparently begun in one of the hepatic ducts and had extended out into the hilus for a few centimeters so that Dr. Wallace could feel it, but it had also involved the cystic duct. Beyond the tumor there was 6 cm. of perfectly normal uninvolved common bile duct. The tumor, which proved to be an adenocarcinoma, had spread through the lymphatics to involve the surface of the body and tail of the pancreas, but the head of the pancreas was perfectly normal.

This patient also had bronchiectasis and a cyst in the tail of the pancreas. There was no evidence of the diffuse cystic disease of the pancreas that is occasionally seen in children and that may be associated with bronchiectasis. In both lower lobes the bronchi were distended to the very periphery of the lobes and contained large quantities of viscid yellowish-green material.

DR. WALLACE: This man, who had an obstructive jaundice, had no chills or fever either at the first admission or at the second, nor did he give a history of any in between times. I wonder if that would have been helpful if that had been brought out.

DR. JONES: I do not know. It is surprising that he did not have elevation of the temperature, because in patients with metastatic or primary involvement of the liver with new growth, fever is frequently an essential part of the picture.

DR. CHAPMAN: As a teacher of physical diagnosis I should like to emphasize, and I am sorry that Dr. Merrill Sosman is not here, that here we have still

another case of bronchiectasis, proved by post-mortem examination, in which x-ray films were negative. Dr. Sosman has in his office at the Peter Bent Brigham Hospital a glass case in which a stethoscope is preserved as a museum piece. I think that we should advise Dr. Sosman to break the glass case and take out the stethoscope, as it still continues to be a valuable instrument in clinical medicine.

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The New England
Journal of Medicine

Formerly
The Boston Medical and Surgical Journal
Established 1828

Owned by the Massachusetts Medical Society and Published under the Jurisdiction of the Committee on Publications

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Material should be received not later than noon on Thursday, two weeks before date of publication.

The Journal does not hold itself responsible for statements made by any contributor.

Communications should be addressed to the *New England Journal of Medicine*, 8 Fenway, Boston 15, Massachusetts.

WHAT SHALL WE DO ABOUT CANCER?

Can we afford to wait for a miraculous cancer cure to appear? Ten million Americans now alive will die of cancer unless we discover methods of therapy that are more effective than those now available. Six million more will die unless our present knowledge is more effectively implemented and applied. Improvements in the therapy of cancer may come by chance, but earnest effort by competent, well-equipped workers will do much to increase such a chance. The limiting factor on cancer research is money, and the limiting factor on dissemination of knowledge about cancer is inertia. Both these bid fair to be removed.

Massachusetts, through its cancer-control program administered by the Department of Public Health and sponsored by the Massachusetts Medical Society, has gone a long way to see that knowledge about cancer is effectively utilized. Even this phase of the task, however, is far from completed.

Funds for cancer research have been woefully inadequate — so inadequate that grants have perforce been limited not only in scope but also in time. Long-range work has been practically impossible. This year the American Society for the Control of Cancer has made a great step forward in initiating in April a nationwide campaign for funds to fight cancer. It is proposed to support research, to disseminate knowledge about cancer and to provide service for cancer sufferers. Not only must this campaign succeed, but research institutions must be established at key points throughout the country; furthermore, these institutions must be supported and staffed in proportion to the importance of the problem to be solved.

PROLONGING THE ACTION OF PENICILLIN

When penicillin is given by mouth, it is largely inactivated in the gastrointestinal tract or remains unabsorbed so that only extremely low levels are attained in the circulating blood and only a small proportion of the ingested drug is excreted into the urine.[1] It has therefore seemed impracticable to use penicillin by the oral route. When given parenterally, penicillin is rapidly excreted into the urine, so that it must be given either by constant intravenous infusion or by frequent intramuscular injection. Each of these methods is objectionable. The constant intravenous drip requires careful regulation of the flow and, hence, constant supervision. It also necessitates the intravenous administration of moderate to large volumes of fluid, which may be undesirable in certain types of patients. Furthermore, thrombosis of the veins occurs quite regularly; this necessitates frequent changing to other veins and also carries with it a not inconsiderable danger from embolism. Thrombosis of the vein during therapy may also interrupt the flow of penicillin unless the condition is recognized

early and the needle reinserted elsewhere. When the intramuscular route is used, absorption is prompt and the drug is rapidly eliminated into the urine so that effective concentrations are difficult to maintain for more than two or, at most, three hours. In severe cases of staphylococcal or *Streptococcus viridans* infections it is often necessary to give 20,000 or 25,000 units every two hours. This means the injection of a volume of 4 or 5 cc. each time, since the use of penicillin in greater concentrations than 5000 units per cubic centimeter often produces excessive local irritation. Furthermore, since it is necessary to repeat the injections throughout the day and night, the patient can have no continuous period of rest, and a physician or trained nurse must always be available to give the injections.

One of the major problems in the use of penicillin, therefore, has been concerned with methods that would simplify its administration both for the patient and for the attending physician and nurses. Several methods have been suggested. These have as their purpose either delaying excretion of the drug by the kidneys or prolonging its absorption from the local site. In either event the attempt is made to maintain an effective level for a longer period after injection or with a smaller amount of penicillin.

One of the methods that has been suggested for accomplishing the first of these purposes involves the principle of "excretory blockade." Rammelkamp and Bradley[3] showed that the excretion of penicillin in the urine was depressed by the simultaneous injection of Diodrast. Para-aminohippuric acid is rapidly excreted by the kidneys and, like Diodrast, has been used in tests of renal function. The former has been used by Beyer and his associates[3] to produce the same result that Ramelkamp and Bradley demonstrated with Diodrast. By intravenous injection of this compound together with penicillin it was found possible to attain and to maintain materially higher concentrations of penicillin in the circulating plasma of animals than are practical without the use of excessive amounts of penicillin. Toxicologic studies indicated that the *p*-aminohippuric acid is nontoxic to mice, rabbits and dogs in the amounts necessary to produce this effect. Previous use of this compound in human beings has been limited to short periods during renal-function tests; hence, the effects of continuous use, particularly in patients with severe infections, is not known, but clinical trials are in progress. No matter how the results of these trials turn out so far as indicating the feasibility of the method or the toxicity of the compound, this type of therapy is obviously not desirable or practical. Although it reduces the dosage of penicillin, it does not obviate the need for constant intravenous infusion. Indeed, careful regulation of the rate of injection of the two compounds simultaneously makes the proper use of this method even more difficult and requires even more constant supervision and control than does the injection of penicillin alone.

Another method involves the intramuscular injection of penicillin in a medium from which it is slowly absorbed. After trials with various oils and other substances, Romansky and Rittman,[4] at the Walter Reed Hospital, have found mixtures of beeswax and peanut oil to be the most satisfactory for this purpose. Preparations of penicillin in this mixture were shown to be quite stable and did not deteriorate when kept at refrigerator, room or body temperature for a period of thirty to sixty-two days. In initial experiments in rabbits, it was found possible to maintain satisfactory levels for six to twelve hours with this mixture, whereas with the same amount of penicillin given in saline solution an effective level was maintained for only two hours. In human subjects, single injections of 41,500 and 66,400 Oxford units were given in 2.0 to 2.4 cc. of the beeswax-peanut oil mixture. Measurable levels were maintained in the blood for six to seven hours, and penicillin was excreted into the urine for twenty to thirty-two hours, indicating that some penicillin was retained in the blood throughout that period. In preliminary trials these workers obtained clinical and bacteriologic cures in 11 of 12 patients with acute gonorrhea by a single injection of penicillin in the beeswax-peanut oil mixture, whereas single injections of a similar amount of penicillin in saline solution were only rarely successful.

A third method that has been suggested involves the use of a continuous intramuscular infusion.[5] Such a continuous drip requires a minimum daily volume of 1000 cc., since it is difficult to control

the rate of flow with smaller amounts of fluid. The flow may be regulated at 12 to 15 drops per minute or 50 cc. per hour and can be adjusted so that the total daily volume delivers 100,000 units of penicillin or any other desired amount. Apparently, the rate of delivery, and hence of the absorption, of penicillin by this method is even more difficult to regulate than with intravenous injections. It has therefore been suggested that the needle be left in situ and that the flow be interrupted at regular intervals. Even with this modification the method is not particularly desirable since it requires considerable manipulation and many adjustments, as well as resulting in local discomfort. Apparatus that permits the continuous daily injection of as little as 100 cc. of a solution has been devised by Scottish workers[6,7] who claim that its use demands little attention.

A simple method of delaying absorption from the ordinary intramuscular injection has been suggested by Trumper and Hutter,[8] of the National Naval Medical Center. These workers have made use of local chilling by means of an ice bag placed over the site of the intramuscular injection for a period of one or two hours before and for five to twelve hours after each injection. A harness is applied to keep the ice bag in place, and the ice is changed every three or four hours. With a single injection of 50,000 to 100,000 units given in this manner they have been able to maintain effective blood levels for five or six hours, as compared with two and a half hours when the same amounts are given intramuscularly without cold applications. By the use of this method cures of acute gonorrhea have been obtained quite regularly with a single injection of 50,000 units of penicillin. This method, however, is cumbersome and does not seem feasible for prolonged therapy.

It is possible that the addition of a vasoconstrictor drug to the penicillin given in a medium in which it is absorbed slowly will result in a further delay of absorption. Adrenalin and longer acting vasoconstrictor drugs, together with gelatin, have been shown to prolong the action of penicillin.[9,10] None of the methods thus far proposed, however, have as yet received adequate clinical trial, particularly in severe infections that require the maintenance of significant blood levels over considerable periods. Furthermore, although they may be somewhat helpful, they do not adequately meet the objections raised to the present methods of administration. It is hoped that simpler methods will be evolved to eliminate the necessity for continuous intravenous injection, which requires constant regulation and involves the danger of thromboses and embolism, or for frequent intramuscular injections, with the resulting discomfort and inconveniences.

While all these methods for prolonging the action of penicillin after parenteral administration are being tried out clinically, progress is also being made toward the development of successful methods of oral administration.[1,11–13] On the basis of reports already available, it seems likely that the ingestion of penicillin in doses larger than those used intramuscularly and in a suitable medium, particularly one that will counteract the acidity of the stomach, will prove feasible.

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MASSACHUSETTS MEDICAL SOCIETY

COMMITTEE ON LEGISLATION

The following copy of Judge Cabot's decision concerning a petition brought by the Trustees of Middlesex University seeking to revise and reverse the decision of the Approving Authority regarding Middlesex University School of Medicine will undoubtedly be of interest to many members of the Society.

WILLIAM E. BROWNE, *Chairman*

COMMONWEALTH OF MASSACHUSETTS

SUFFOLK, ss: SUPERIOR COURT
No. 393180

IN RE THE TRUSTEES OF MIDDLESEX UNIVERSITY

Findings, Rulings and Order for Decree

This is a petition brought by the Trustees of Middlesex University under the provisions of General Laws, Chapter 112, Section 2, as amended by Statute 1936, Chapter 247, seeking to "revise and reverse the decision of the Approving Authority" created by that statute. The petitioner is a corporation chartered by statute in 1937 and operates a medical school called the Middlesex University School of Medicine (hereinafter usually referred to as Middlesex). Although no party respondent is named in the petition, an order of notice was issued to Dr. H. Quimby Gallupe, secretary of the Board of Registration in Medicine, and the Approving Authority, appeared by the Attorney General, and the proceeding was conducted as an adversary one against that body with full scope to each to cross examine witnesses, introduce evidence and in general to be heard as would opposing parties in a suit in equity.

In the first place, it is pertinent to examine briefly the statute above referred to so that the nature of the proceeding should be made clear. The act makes it a condition precedent to the right of any person to take the examination to become a licensed physician that he shall have received a degree of doctor of medicine from an "approved" medical school. Paragraph two of the act allows any medical school to request the Approving Authority to make an inspection of it whereupon it becomes the duty of that body to inspect and either approve the school or notify it what steps it must take in order to gain approval. It is to be noted that there is no provision under this paragraph for a final determination of disapproval. The next paragraph of the act gives a school the right to request approval from the Approving Authority and it then becomes the duty of the latter, after holding a public hearing, to approve or disapprove. It is to be noted that there is no duty imposed upon the Approving Authority either to make an inspection or a decision as to approval unless so requested although, on the other hand, there is no prohibition to its granting approval without a request. Thus, a school may request inspection, in which case it may receive either approval or a direction as to what it must do to gain approval without incurring the risk of a final decision. Only after the school itself requests a final decision does it incur the risk of disapproval. Only after such final decision of disapproval or withholding approval does the school have the right to file a petition in the court to "revise and reverse the decision of the Approving Authority." The statute as finally extended became operative as to persons who entered a medical school on or after January 1, 1941.

Middlesex first requested an inspection in May, 1941. Pursuant to this request the Approving Authority made an inspection on May 28, 1941, and by letter dated August 1, 1941, notified Middlesex that in order to gain approval it would have to take the following steps:

(1) Its Board of Trustees shall be reorganized so that the management and control of the medical school shall be vested in trustees who are unquestionably qualified to manage, control and administer such an important institution as a medical school.

(2) The dean shall be one who is recognized as having had experience in the broad field of medical education and who possesses executive and administrative ability.

(3) The medical school shall have financial resources adequate for providing medical education which meets generally accepted present-day standards.

(4) There shall be a faculty of which a majority of the members thereof have attained such eminence in their profession that they are so recognized by their fellow workers in their specialties.

(5) There shall be adequate clinical material available for teaching purposes for all branches of medicine, with special emphasis on medicine, surgery, pediatrics and obstetrics.

(6) The facilities, both in space and equipment, for research shall be substantially increased.

Early in 1943, Middlesex again requested an inspection, which was made on April 2 and May 25, 1943, and by letters dated June 25 and July 23, 1943, the Approving Authority notified it that it was deficient in the following respects:

(1) Although the administrative organization and personnel have undergone changes, they are still inadequate for accomplishing the objectives of the institution.

(2) The medical school has not the financial resources to provide adequate medical education.

(3) The faculty falls below acceptable standards in numbers and quality.

(4) There are insufficient clinical facilities for the teaching of the various branches of medicine.

(5) The facilities in the Library are inadequate in number and selection.

Again on June 20, 1944, the Approving Authority inspected the school pursuant to its request, and by letter dated July 13, 1944, notified it that the following steps were necessary in order to gain approval:

(1) That the quality and number of the faculty should be improved.

(2) That the amount of clinical material available for teaching purposes should be increased.

(3) That the financial resources of the medical school are not sufficient to provide adequate education and that these resources should be greatly increased.

(4) That the administrative organization and personnel is still inadequate for accomplishing the objectives of the institution.

At some time shortly before July 17, 1944, Middlesex filed, with the Approving Authority, a written request for approval. Thereupon a hearing was set for July 17, 1944, Middlesex was duly notified, and the hearing was held on that date in the Gardner Auditorium in the State House where all persons desiring to be heard were heard. Middlesex was represented by its attorney who presented such persons as he desired to present the case of the school for approval. Other persons gave their views, and although they were not cross examined by the attorney for Middlesex, there is nothing to indicate that he could not have done so had he desired. The hearing was more in the nature of those that are commonly held by the committees of the legislature than of the kind familiar in judicial proceedings. By letter dated July 20, 1944, the Approving Authority notified Middlesex that "the Middlesex University Medical School is not approved by the Approving Authority for the purposes of Section 2 of Chapter 112 of the General Laws as amended." It is this decision that this petition filed in this court on August 16, 1944, seeks to "revise and reverse."

The statute provides that "the court shall hear the case and finally determine whether or not such approval shall be granted or revised." Inasmuch as there can be a petition in this court only if approval is denied by the Approving Authority it is difficult, if not impossible, to understand how "such approval" can be "revised" even if that word is construed as "review" as it was in a different statute in Ott v. Board of Registration in Medicine, 276 Mass. 566. It is not so difficult to give effect to the word "revise" as it is used in that portion of the statute which gives an institution aggrieved by an adverse decision of the Approving Authority the right to file a petition "to revise or reverse the decision of the approving authority." Here a construction of the word "revise" as "review" would indicate that the jurisdiction of this court is limited to a re-examination of proceedings already had before the Approving Authority rather than an entire retrial such as would arise on appeal. The point need not be decided, however, because from the outset of the trial before me the parties were fully heard both upon the aspect of a review of the proceedings already had and a trial of the merits of whether Middlesex should be approved or not and because my decision is the same whichever is the proper construction of the statute.

A review of the proceedings of the Approving Authority indicates no reason why its decision should be revised or reversed. A public hearing was held seasonably after the request for approval was filed by Middlesex, which was given due notice of it and was heard without restriction. Within twenty

days after the hearing it made its decision in writing and notified Middlesex of such decision. The statute requires nothing more. On the other hand, it does not limit the Approving Authority to a consideration of such matter as may be brought out in the public hearing. Obviously, it might, and in fact it did, consider the information it had gained from its three previous inspections of Middlesex. From its inspections and study of other medical schools both within and without this commonwealth it had a basis for a comparison of the medical education given at those schools with that given at Middlesex. Two of the members of the Approving Authority are themselves licensed practitioners of medicine and by the very nature of their official positions are presumed to be and in fact are well qualified to judge the kind of education necessary to produce an adequately trained doctor. The third member, although not a specialist in the field of medical education, is a specialist in the field of general education. Both he and the other members of the board are by training and experience far better qualified to pass on the merits of medical education than is this court. They acted fairly and conscientiously and with rigorous regard to the provisions of the statute under which they acted. If this be merely a proceeding to review the proceedings of the Approving Authority its decision must stand.

If the jurisdiction of this court is not limited to a mere review of the proceedings of the Approving Authority but includes an entire retrial of the issue as to whether Middlesex be approved or not the decision must be the same. The statute lays down neither for the Approving Authority nor this court any guide by which approval should be granted or withheld. Obviously, however, it is designed to make sure that the people of this commonwealth get as good medical care as possible and the fundamental consideration must be that all persons who are licensed to practice medicine are adequately trained for that purpose. It is equally obvious that the purpose of the statute was not to allow as many medical schools to exist (and it is hard to see how one could exist for many years without approval) as there may be students who would like to attend unless such schools give an adequate medical education. The Legislature has recognized that the mere passing of an examination is not a sufficiently adequate basis on which to allow one to practice medicine and has therefore provided that a prerequisite to taking the examination must be a proper premedical and medical training. Whether the training which any particular school may give is adequate must in great part depend upon a comparison with the training that other schools give. It must be judged in the light of present-day standards of medical education having due regard to the number of doctors needed to adequately care for the health of the residents of the Commonwealth. Not only the best school or schools are entitled to approval, but somewhere the line must be drawn between a school which is sufficiently adequate and one that is not. A school which years ago might have been the best in the country would not today, had it not kept reasonably abreast of general improvement, be entitled to approval. My decision is, therefore, primarily based upon a comparison with other medical schools concerning which evidence was produced. These were primarily the medical schools of Boston University, Harvard and Tufts.

It would serve no useful purpose to recount these very considerable number of aspects which might, standing by themselves, entitle Middlesex to approval, for there are three aspects in which it is fatally deficient. Nor would it be helpful or material to point out the difficulties Middlesex has had in overcoming these deficiencies in spite of a very genuine attempt in recent years to improve its standards. Nor is it material to consider what it might be in months or years hence even though it be recognized that the very fact of approval would remove some of the obstacles with which the school is faced in its attempt to improve itself. Middlesex, not the Approving Authority or this court, chose the time at which it would seek approval and this court must view it as it now is and not as it has been or may become.

The fatal deficiencies are these:

(1) The school has not adequate financial backing. Substantially all of its income is derived from tuition fees paid by students. These are $450 per year per student, which is not out of line with the tuition fees in other schools, Tufts being $500, Boston University $475 and Harvard $400. But each of these other schools by reason of having other income available spends per year much more than the amount of the tuition, the lowest spent by any of the above three schools being something more than $800 per year per student. Middlesex, on the other hand, for the year ended June 15, 1944, had a total income, all from tuition fees, of $190,106.30 and spent $180,919.10 including the sum of $45,271.61 for administrative expense, which is abnormally high compared, for example, with about $15,000 administrative expense for Boston University. I am satisfied and so find that, unless there are some unusual circumstances not here present, it is necessary for a medical school to spend an amount in the neighborhood of $800 per year per student in order to give a proper medical education.

The graduates of Middlesex have in the past year collected some $50,000 for its use, but only $5000 has so far been actually turned over to the school. They hope to raise $50,000 per year hereafter, but so far that is a hope rather than a reality. A parents' association has raised some $200,000, but this is to be turned over to the school only if it receives approval. Regardless of what the future may hold the present financial backing of the school is far below what is necessary to give an adequate medical education.

(2) The quantity of the faculty is not sufficient. The school has in recent years been able to obtain for its teaching staff a number of European refugees who are well qualified in their particular fields. By and large the qualifications of its teaching staff are satisfactory. It is in numbers that it is deficient. At present there are 45 teachers for a student body of about 340. This compares with Harvard having 487 teachers for 525 students, Tufts 433 for 404 students, and Boston University 190 for 255 students. The chief difficulty in obtaining more teachers is again financial. Middlesex uses too high a proportion of its available funds for administrative expense and does not have sufficient funds to hire a sufficient number of teachers. Clearly 340 medical students cannot be adequately trained by a teaching staff of 45.

(3) The most serious deficiency of all is Middlesex's almost complete lack of clinical facilities for teaching. The modern method of teaching medical students is in great part the observation of sick patients under the guidance of a doctor who is not only a trained practitioner but a teacher as well. In order to do this a medical school must have a connection with one or more hospitals having a sufficient number of so-called "teaching beds." The typical curriculum of a medical school involves for the first year lectures, laboratory work and general demonstrations in hospitals; for the second year the same as the first with the addition of some clinical teaching in hospitals; for the third year almost entirely clinical teaching; and for the fourth year entirely clinical teaching. Frequently, indeed usually, the teacher appointed by the medical school and on its faculty also holds an appointment on the staff of the hospital. Thus he has a double duty — to care for patients in the hospital and to instruct groups of students who go with him as he sees these patients on his rounds. A very large number of "teaching beds" is required both because the students have to be taught in small groups and because a small number of beds would not produce a sufficient variety of human ailments. Harvard, for example, for its 525 students has 1872 "teaching beds," and Tufts and Boston University on a comparable basis somewhat less. The only hospital with which Middlesex has a similar connection and where persons are paid by it to instruct students at the bedside is the Brockton Hospital, which has a total of 45 "teaching beds." Fourth-year students at Middlesex each have about two weeks' training at this hospital and they also have a short period as "clinical clerks" in a number of other small hospitals. A "clinical clerk" does certain elementary examinations at hospitals and generally assists practicing doctors and interns in those hospitals. Although these "clinical clerks" from Middlesex usually act under the supervision of "clinical preceptors" those persons are not employed by or on the teaching staff of the school and have no actual responsibility for the training of the students. Without doubt these "clinical clerkships" are of value to the student but they fall far short of the value received from organized teaching in hospitals. Middlesex has made strenuous efforts to improve its facilities for clinical teaching but has had little success due to various obstacles not the least of which being the fact that it is not an approved school. The fact remains, however, that at the present time its clinical facilities are grossly inadequate for proper medical education.

Although I have treated this petition as a matter sounding in equity, it is not clear whether it is a proceeding in equity or one at law. In order, therefore, to adequately protect the rights of the parties I pass upon their requests for rulings of law as follows:

The petitioner's requests numbered 1, 2, 3, 4, 5, 16 and 17 are denied and all others granted. The requests of the Approving Authority are all denied.

A decree may issue affirming the decision of the Approving Authority.

CHARLES C. CABOT
Justice of the Superior Court

January 5, 1945

SUPPLEMENTAL FINDINGS OF FACT

In the document entitled "Findings, Rulings and Order for Decree" it is stated, "Middlesex, not the Approving Authority or this court, chose the time at which it would seek approval." Nothing in these supplemental findings is intended to modify that statement. It is, however, clear that Middlesex chose the summer of 1944 as the time to ask for approval in order that the students might be able to file applications to take the examination to become licensed physicians which was to be held in November of 1944.

The class graduating from Middlesex in July, 1944, embraced in major part the first students who had originally matriculated in the school after January 1, 1941. The graduation of these students would normally have taken place in June or July of 1945, but because the school had, in common with other medical schools by reason of war exigencies, accelerated its program, the course for these students was completed in July of 1944. Thus, the adoption by the school of the accelerated program deprived it of additional time which it would otherwise have had before asking for approval to enable those students who matriculated on or after January 1, 1941, to take the state examinations and thus it was also deprived of almost a year in which to continue to endeavor to improve the standards of the school.

CHARLES C. CABOT
Justice of the Superior Court

January 17, 1945

COMMITTEE ON POSTWAR PLANNING

On March 7, a meeting of the Committee on Postwar Planning heard a report from the Subcommittee on Hospitals that comprised a consideration of the requirements for hospitals providing internships and residencies in the postwar era. It is recognized that many hospitals in the Commonwealth badly need interns and residents and wish to organize staff personnel to provide the proper educational experience for such men. The Committee on Postwar Planning is eager to receive questions and suggestions in this field and will gladly communicate with hospital representatives or appropriate committees of district societies.

HOWARD F. ROOT, *Chairman*
LEROY E. PARKINS, *Secretary*

NEW HAMPSHIRE MEDICAL SOCIETY

DEATHS

HAWKINS — Frederick L. Hawkins, M.D., of Meredith, died November 8. He was in his eighty-fourth year.

Dr. Hawkins received his degree from Jefferson Medical College of Philadelphia in 1886. He was a member of the Belknap County Medical Society and the New Hampshire Medical Society.

His widow survives.

NORMANDIN — Armand Normandin, M.D., of Laconia, died February 14. He was in his fifty-ninth year.

Dr. Normandin received his degree from the University of Montreal in 1911. He was a member of the Belknap County Medical Society, the New Hampshire Medical Society and the American Medical Association. He retired from active practice in 1944.

His widow, three sisters and three brothers survive.

OBER — Charles F. Ober, M.D., of Manchester, died January 29. He was in his ninety-seventh year.

Dr. Ober received his degree from New York University Medical College in 1879. He was a member of the New Hampshire Medical Society and the American Medical Association.

His brother survives.

NOTICES

AMERICAN BOARD OF OBSTETRICS AND GYNECOLOGY

The general oral and pathological examinations (Part II) for all candidates will be conducted at Atlantic City, New Jersey, by the entire Board from Thursday, June 14, through Tuesday, June 19, 1945. The Hotel Shelburne will be the headquarters for the Board. Formal notice of the exact time of each candidate's examination will be sent him several weeks in advance of the examination dates. Hotel reservations may be made by writing direct to the hotel.

Candidates for re-examination in Part II must make written application to the secretary's office not later than April 15.

The Office of the Surgeon General of the United States Army has issued instructions that men in service, eligible for Board examinations, be encouraged to apply and that they may request orders to detached duty for the purpose of taking these examinations whenever possible. Candidates in military or naval service are requested to keep the secretary's office informed of any change in address.

Deferment without time penalty, under a waiver of the published regulations applying to civilian candidates, will be granted if a candidate in service finds it impossible to proceed with the examinations of the Board. Applications are now being received for the 1946 examinations. For further information and application blanks, address Dr. Paul Titus, Secretary, 1015 Highland Building, Pittsburgh 6.

TUFTS MEDICAL ALUMNI ASSOCIATION

The annual dinner meeting of the Tufts Medical Alumni Association will be held on Wednesday, April 11, at the Copley Plaza Hotel, Boston. The committee on arrangements consists of Dr. James W. Manary, chairman, Dr. Harry Blotner, secretary-treasurer, and Drs. Carl Bearse, William E. Browne, Hilary J. Connor, Roy J. Heffernan and Frank Ober.

The guest speaker will be Senator Claude Pepper, who will speak on the subject "The Findings and Recommendations of the Senate Subcommittee on Wartime Health and Education," of which he is chairman. Other speakers will include Dr. A. K. Paine, professor of obstetrics, Dr. Louis E. Phaneuf, professor of gynecology, Captain A. Warren Stearns, dean-on-leave, Dr. Dwight O'Hara, acting dean, Dr. Benedict F. Boland, clinical professor of gynecology, and Dr. Leonard Carmichael, president of Tufts College.

NEW ENGLAND DERMATOLOGICAL SOCIETY

The regular and annual meeting of the New England Dermatological Society will be held in the Skin Out-Patient Department of the Boston City Hospital on Wednesday, April 11, at 2 p.m.

NEW ENGLAND HOSPITAL FOR WOMEN AND CHILDREN

The monthly clinical conference and meeting of the staff of the New England Hospital for Women and Children will be held on Thursday, April 5, at 7:15 p.m. in the classroom of the Nurses' Residence. Dr. Bianca R. Lia will speak on the subject "Lipiodol Study of the Uterus and Tubes."

(*Notices continued on page xvii*)